13-1342

IN THE

United States Court of Appeals

FOR THE FEDERAL CIRCUIT

BUTAMAX(TM) ADVANCED BIOFUELS LLC,

Plaintiff-Appellant,

—v.—

GEVO, INC.,

Defendant-Appellee.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE
IN NO. 11-CV-0054
JUDGE SUE L. ROBINSON

BRIEF FOR PLAINTIFF-APPELLANT BUTAMAX(TM) ADVANCED BIOFUELS LLC [NON-CONFIDENTIAL]

LEORA BEN-AMI
THOMAS F. FLEMING
CHRISTOPHER T. JAGOE
PETER B. SILVERMAN
KIRKLAND & ELLIS LLP
601 Lexington Avenue
New York, New York 10022
(212) 446-4800

Attorneys for Plaintiff-Appellant Butamax(TM) Advanced Biofuels LLC

CERTIFICATE OF INTEREST

Pursuant to Federal Circuit Rules 26.1, 28(a)(1) and 47.4, counsel for Plaintiff -Appellant Butamax™ Advanced Biofuels LLC certifies the following:

1. The full name of every party or amicus represented by me is: Butamax™ Advanced Biofuels LLC.

2. The name of the real party of interest represented by me is: None.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are: E.I. du Pont de Nemours and Co. and BP Biofuels North America LLC.

4. The names of all law firms and the partners or associates that appeared for the party now represented by me in the trial court or are expected to appear in this Court are:

Kirkland & Ellis LLP
Leora Ben-Ami
Thomas F. Fleming
Patricia Carson
Christopher T. Jagoe
William Cory Spence
Daniel Forchheimer
Peter B. Silverman

Kaye Scholer
Hank Heckel
Abigail Langsam
Richard A. De Sevo

Potter Anderson & Corroon, LLP
Richard L. Horowitz
David Ellis Moore

Respectfully submitted,

/s/ Peter B. Silverman

May 31, 2013

Leora Ben-Ami
Thomas F. Fleming
Christopher T. Jagoe
Peter B. Silverman
KIRKLAND & ELLIS LLP
601 Lexington Avenue
New York, NY 10022
Telephone: (212) 446-4800

Counsel for Plaintiff-Appellant Butamax™ Advanced Biofuels LLC

TABLE OF CONTENTS

CONFIDENTIAL MATERIAL OMITTED

Confidential material has been omitted from pages 25, 26, 27, 28, 39, 40, 56 and 57 of this Opening Brief. That information relates to the subject matter of the Statement of the Facts Section II.A, Argument Sections IV.A.1 and V. and contains excerpts from documents produced by Defendant-Appellee Gevo, Inc. and filed under seal with the district court pursuant to the Protective Order entered on July 18, 2011.

TABLE OF AUTHORITIES

Cases

Statutes

Rules

STATEMENT OF RELATED CASES

An earlier appeal was taken from the district court's denial of Butamax™ Advanced Biofuels LLC's ("Butamax") motion for a preliminary injunction against Gevo Inc., ("Gevo"), before Chief Judge Rader, and Circuit Judges Dyk and Wallach, with a decision issuing on Nov. 16, 2012. *Butamax(TM) Advanced Biofuels LLC v. Gevo, Inc.*, 486 F. App'x 883, 883 (Fed. Cir. 2012).

The patents at issue in this appeal are U.S. Patent No. 7,993,889 (the "'889 patent), which is subject to a pending *inter partes* reexamination, No. 95/001,735 and a pending *ex parte* reexamination, No. 90/012,503, and U.S. Patent No. 7,851,188 (the "'188 patent), which is also subject to a pending *inter partes* reexamination, No. 95/001,857.

A continuation of the '188 and '889 patents (collectively the "Butamax Patents"), U.S. Patent No. 8,178,328, is in suit in *Butamax™ Advanced Biofuels LLC v. Gevo, Inc.*, Civil Action No. 12-602-SLR (D. Del.). A continuation of the '188 and '889 patents, U.S. Patent No. 8,283,144, is in suit in *Butamax™ Advanced Biofuels LLC v. Gevo, Inc.*, Civil Action No. 12-1300-SLR (D. Del.). A continuation-in-part of the '188 and '889 patents, U.S. Patent No. 8,273,558, is in suit in *Butamax™ Advanced Biofuels LLC v. Gevo, Inc.*, Civil Action No. 12-1200-SLR (D. Del.). Counsel for Butamax is not aware of any

other case pending in this or any other court that will directly affect or be directly affected by this Court's decision in this appeal.

STATEMENT OF JURISDICTION

The district court has subject matter jurisdiction under 28 U.S.C. §§ 1331 and 1338(a) and entered an amended final judgment on April 10, 2013. On April 19, 2013, Butamax timely filed a Notice of Appeal. 28 U.S.C. § 2107(a); Fed. R. App. P. 4(a)(1)(A). This Court has exclusive jurisdiction under 28 U.S.C. § 1295(a)(1).

PRELIMINARY STATEMENT

Despite this Court's admonition on the prior appeal that "the trial court should reconsider its construction" of the term "acetohydroxy acid isomeroreductase," (hereinafter the "KARI element")[1] on remand the district court essentially maintained its "very questionable construction," attempting to buttress it with improper extrinsic evidence. In so doing, the court ignored the plain meaning of the disputed term and the bulk of the specification, and rendered several dependent claims of the patents meaningless.

As it had done before, the court narrowed the KARI element, importing a limitation into the claim, and finding a subset of KARIs to be excluded by misapplying the "lexicography doctrine." Further, the court rendered the KARI element indefinite by reading in the term "dependent," compounding the error.

[1] The term "KARI" refers to "acetohydroxy acid isomeroreductase." As Gevo and its expert previously admitted, "[i]t is undisputed" that these terms are interchangeable. A03104, n.9.

Ultimately, the court fundamentally misunderstood the purpose of the specification's description of the enzymes. In particular, the court read the specification's description of KARI—which was based on a seminal test to identify that enzyme by use of a given cofactor—to redefine the enzyme. In so doing, however, the court imported a negative limitation on KARI that excludes enzymes that can be identified by that test, but may also use other cofactors. From this flawed logic, the court narrowly construed the term at odds with its plain meaning and the specification's description of that enzyme.

Once the proper plain meaning construction is applied then literal infringement inexorably follows. Gevo's documents clearly show its products meet every limitation of the asserted claims. Even for the KARI element, the undisputed evidence shows Gevo's KARIs catalyze the reaction required by the claims, is virtually identical to KARI sequences disclosed in the Butamax Patents, and has KARI activity in a standard test disclosed in the specification.

The district court's grant of summary judgment of non-infringement under the doctrine of equivalents ("DOE") falls with its erroneous claim construction. Even under that construction, the court erred in its DOE ruling by analyzing features that are not part of the claimed invention, and by disregarding Butamax's substantial evidence showing the disputed enzymes are equivalent to the KARI element as construed. Reviewing that evidence under the appropriate

legal standard, Butamax proffered sufficient evidence by which a reasonable jury could rule in its favor.

In finding claims 12 and 13 of the '889 patent invalid due to lack of written description on summary judgment, the district court further erred by dismissing disclosures of the specification, evidence from Butamax's experts and Gevo's own experts' admissions, who testified the specification "completely" described the claimed invention. Thus, there was more than sufficient evidence to withstand summary judgment. Finally, in an apparent scrivener's error, the court's order states that these claims are invalid for lack enablement. This too must be reversed, as Gevo did not move on this basis, and the opinion does not address that issue.

Once the district court's rulings are corrected, the denial of Butamax's motion for summary judgment of infringement cannot stand. This Court should therefore reverse the claim construction ruling and direct the entry of judgment of literal infringement by Gevo, reverse the no DOE and invalidity rulings and remand for further proceedings.

STATEMENT OF THE ISSUES

1. Whether the district court erred in construing "acetohydroxy acid isomeroreductase" to mean a "NADPH-dependent" enzyme, where the specification states it is an enzyme which catalyzes a conversion "using NADPH" "as an electron donor," referring to an in vitro assay set out in the specification, as confirmed by the prosecution history, and where the court conceded that it could not discern the metes and bounds of its substituted term "NADPH-dependent."

2. Whether the district court erred in denying Butamax's summary judgment of literal infringement, where the only disputed element in Gevo's product—the "acetohydroxy acid isomeroreductase" enzyme—meets the plain meaning of this term, and has the enzymatic activity in the in vitro assay referenced in the specification.

3. Whether the district court erred in granting Gevo's motion for summary judgment of non-infringement under DOE, where the court based its DOE ruling on features that are not part of the claimed invention, disregarded substantial evidence showing the disputed enzymes are equivalent to the enzyme recited in the claim, and where Gevo's motion was based only on prosecution history estoppel.

4. Whether the district court erred in granting Gevo's motion for summary judgment of invalidity of claims 12 and 13 of the '889 patent for lack of

written description, where Gevo's expert acknowledged that the specification's disclosures "completely" described the claimed invention, and Butamax proffered more than sufficient evidence by which a jury could rule on its behalf?

5. Whether the district court erred in its order granting summary judgment that claims 12 and 13 of the '889 patent are invalid for lack of enablement, when the parties did not brief that issue, and the court's memorandum did not discuss that issue?

STATEMENT OF THE CASE

On January 14, 2011, Butamax sued Gevo in the United States District Court for the District of Delaware for infringement of the '188 patent.[2] On August 9, 2011, the '889 patent issued—a divisional of the '188 patent—and Butamax filed an amended complaint on August 11, 2011 also alleging infringement of that patent.[3]

Butamax moved for a preliminary injunction based only on the '889 patent on September 22, 2011.[4] The district court denied Butamax's motion,[5] which Butamax appealed on June 25, 2012.[6] Although this Court affirmed, it stated that "should not be read to endorse the trial court's very questionable construction of the claim term 'acetohydroxy acid isomeroreductase'—that is 'as an enzyme that is solely NADPH dependent.'"[7] The Federal Circuit specifically stated the trial court should "reconsider its construction when it holds a *Markman* hearing."[8]

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[2] A00069.

[3] A00074.

[4] A00076.

[5] A00109.

[6] *Id.*

[7] *Butamax(TM) Advanced Biofuels LLC v. Gevo, Inc.*, 486 Fed App'x 883, 883 (Fed. Cir. 2012).

[8] *Id*.

The district court held a *Markman* hearing on the Butamax Patents on January 18, 2013. This Court's Order notwithstanding, counsel for Gevo argued at that hearing that the "Federal Circuit fundamentally agreed with your construction despite Butamax's efforts to suggest otherwise."[9]

Months later, on the eve of trial, the district court issued its Memorandum Opinion, construing the term "acetohydroxy acid isomeroreductase" (KARI) in substantially the same manner as before, to mean "an enzyme known by the EC number 1.1.1.86 that catalyzes the conversion of acetolactate to 2,3-dihydroxyisovalerate and is NADPH-dependent."[10] The court stated that it "does not find a quantification for this term"—referring to "dependent"—"in the parties' documents and, therefore, does not define it herein, but leaves the explanation of this term of art at trial to the parties' scientific experts."[11] At the pretrial conference, the court confirmed that it created three subcategories of KARIs—NADPH-dependent, NADH-dependent, and NADH-, NADPH-dependent (hereinafter "dual dependent")—and narrowed the KARI element to only the NADPH-dependent category, as it had when construing the term during the preliminary injunction denial.[12]

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[9] A10781, 31:25-32:2.

[10] A00022.

[11] A00040, n.25.

[12] *Compare* A10831, 11:6-12, *with* A04480.

The district court further determined that cofactors NADPH and NADH are "[not] insubstantially different" and therefore there can be "no plausible doctrine of equivalents argument," although the independent claims do not have a limitation to any cofactor.[13] The court granted in-part Gevo's motion for invalidity of the '889 patent, finding claims 12 and 13 invalid for lack of written description,[14] and also ordered those claims invalid for lack of enablement without opinion or notice to Butamax, and without Gevo moving on this basis.[15]

In light of the district court's claim construction, Butamax stipulated to no literal infringement on April 3, 2013.[16] The court entered an amended final judgment on April 10, 2013.[17] Butamax filed its notice of appeal on April 19, 2013.[18]

It must be noted at the outset, because the district court defined KARI as "NADPH-dependent," Butamax uses this term herein to explain why that construction is erroneous and conflicts with the intrinsic evidence. However, the court itself failed to define this term other than by what it is not— *i.e.*, *not* NADH-

[13] A00041 & n.27.

[14] A00054-A00055.

[15] A00059.

[16] A10758-A10762.

[17] A00144.

[18] *Id.*

dependent, *not* dual dependent and *not* ancillary activity using NADPH.[19] The court also failed to define what constitutes "ancillary activity." Importantly, the Butamax Patents do not speak of KARI in terms of cofactor "dependency," nor do they refer to enzyme activity as "ancillary" or "non-ancillary." Thus, to the extent Butamax discusses the term "dependent," we use that term as used by the district court, understanding that this meaning itself is not clear, given the court's lack of guidance on "dependent" and "ancillary activity," and lack of support for these terms in the specification.

STATEMENT OF FACTS

I. Butamax Pioneered Genetically Engineered Microorganisms that Make Isobutanol

The Butamax Patents cover the pioneering invention of recombinant microorganisms engineered to express a biosynthetic pathway for producing isobutanol—a revolutionary, renewable technology that will reduce greenhouse gas emissions, dependence on foreign oil and move the fuel industry into the 21st century.[20]

[19] A00020, n.14 ("By 'use,' the court refers not to ancillary activity, but that the enzyme is NADH- or NADPH-dependent.").

[20] A00149, 1:20-40.

From fuel shortages in the 1970s through the surge in oil prices this past decade, the need for renewable fuel has been clear.[21] In 2003, E.I. du Pont de Nemours and Co. ("DuPont") and BP America, Inc. sought to address that need. After numerous meetings and analyses, their focus turned to creating genetically engineered microorganisms to produce isobutanol, a renewable biofuel with excellent fuel properties.[22] By 2006, DuPont invented and reduced to practice several kinds of recombinant microorganisms that express an engineered pathway to make isobutanol in substantial amounts.[23]

That technology is described in applications that matured into the Butamax Patents, which were later assigned to Butamax.[24] Butamax was formed in 2009 as a joint venture between DuPont and BP Biofuels North America LLC to commercialize this new, sustainable technology.[25]

A. Butamax's Engineered Pathway

In 2005, engineering microorganisms to express several enzymes in a coordinated manner was an unpredictable art.[26] Nonetheless, the Butamax inventors conceived and reduced to practice several multi-step, engineered

[21] A10451-A10453.

[22] A00530; A00537; A00978; A00984-A00985; A01283-A01291.

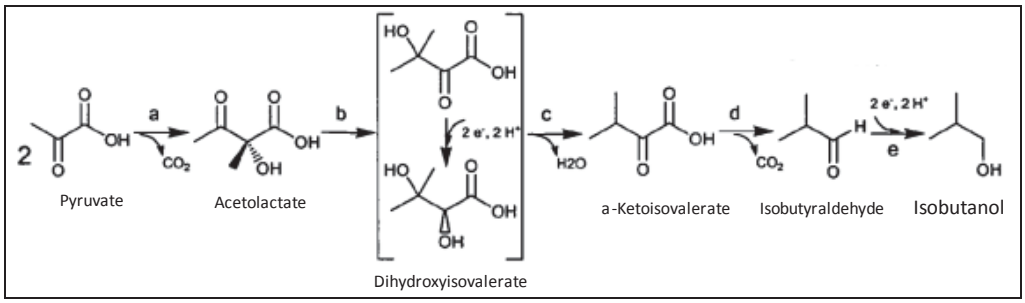
[23] A00169-A00176.

[24] A00147; A00321.

[25] A00530; A00982.

[26] A10394-A10395.

pathways in various microorganisms.[27] Like an assembly line, these pathways work by making the product of one enzyme the substrate for the next enzyme, and so on down the line, until isobutanol is formed. The inventors selected one preferred engineered pathway as the subject of their claimed invention, which has five substrate-to-product conversions from steps a-e[28]:



Each conversion is catalyzed by a different class of enzyme, which can be expressed from genes inserted into a microorganism.[29]

1. The Claimed Engineered Pathway Comprises Five Classes of Enzymes

Enzymes are proteins that catalyze the conversion of a substrate to a product.[30] Persons of skill in the art ("POSA") categorize enzymes into classes based on the reaction they catalyze.[31] While enzymes from different organisms may have different sequences, POSAs refer to enzymes by the same name/class if

[27] A00149-A00150.

[28] A00148 (annotations added).

[29] A00150-A00151; A00153, 9:63-10:16.

[30] A01285-A01286.

[31] A01286.

they can catalyze the same reaction.[32] When different enzymes share sequence identity or "homology" with a classified enzyme, POSAs may correlate that structure with the function of the class,[33] and may test that function in published assays.[34] Because the critical feature of Butamax's engineered pathway is the production of isobutanol through the five-step substrate-to-product conversions, the pathway relies on classes of enzymes at each step rather than requiring any particular enzyme, comprising: a) acetolactate synthase (ALS); b) acetohydroxy acid isomeroreductase (KARI); c) acetohydroxy acid dehydratase (DHAD); d) decarboxylase, (e.g. KIVD); and e) alcohol dehydrogenase (ADH).[35]

The inventors describe making isobutanol under various fermentation conditions, with anaerobic conditions being preferred,[36] and also teach that to maximize isobutanol production it is necessary to "inactivate competing pathways for carbon flow by deleting various genes" that may be expressed naturally.[37] For example, wild-type yeast make ethanol from pyruvate via an enzyme called

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[32] *Id*.; A07058-A07059.

[33] A01286.

[34] A00165, 33:6-9, 33:45-48, 34:17-19, 34:50-53; A00166, 35:22-25.

[35] A00154, 12:1-18.

[36] Aerobic means in the presence of oxygen, and anaerobic means in its absence. A00160, 24:22-25. It is well known that in yeast cells, under anaerobic conditions, NADH is more abundant than NADPH, which are closely related cofactors discussed further below. A04578-621, at A04596.

[37] A00158, 19:24-26.

pyruvate decarboxylase (PDC). The engineered pathway also uses pyruvate as a starting material, and so active PDC enzymes steal pyruvate away from the engineered pathway. Thus, the inventors instruct that to "prevent misdirection of pyruvate away from isobutanol production," PDC should be replaced with a recombinant enzyme called KIVD.[38] The specification then provides KIVD examples to be used.[39]

As the KARI element is the critical dispute on appeal, the following focuses on that enzyme class.

2. The Function and History of KARI Enzymes

KARI enzymes catalyze the conversion of acetolactate (AL) to 2,3 dihydroxyisovalerate (DHIV).[40] This conversion involves two different reactions: isomerization (which changes the arrangement of atoms, but not the composition of atoms in a substrate) and reduction (which adds electrons to the substrate).[41] KARI uses an electron donor, often called a "cofactor," to supply electrons for the reduction noted in the figure below.[42]

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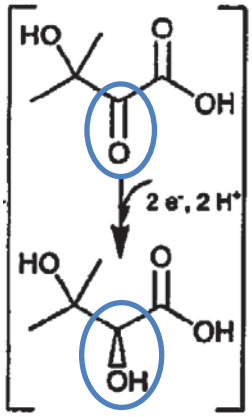
[38] A00154, 12:40-50.

[39] *Id.*

[40] *Id.*, 12:10-12.

[41] A04594, ¶35.

[42] *Id.*, A00148 (annotations added).



Two closely-related cofactors called NADH and NADPH are electron donors that naturally exist in cells.[43] In chemical terms, the difference between these cofactors is trivial: "NADPH has an extra phosphate group on a part of the molecule that is far from the active region."[44] In natural cell metabolism these cofactors are used for different systems, but in terms of donating electrons they are functionally equivalent.[45]

KARI enzymes have been a subject of interest for many years. In the 1960s a unit of KARI activity was defined in a paper by Arfin and Umbarger (1969).[46] These authors purified a KARI enzyme from nature, described the substrate-to-product conversion, and provided an assay to quantify KARI

[43] A04594, ¶35.; A00154, 11:59-65.

[44] A04594, n.9; A05373-A05376; A10564, 279:25-280:25.

[45] A05373-A05376; A04594, ¶35.

[46] A04825 ("One unit of isomeroreductase activity is defined as the amount required to oxidize 1 µmole of NADPH per minute under standard assay conditions.").

activity.[47] That assay (the "Arfin assay") became the standard means in the field for identifying a KARI enzyme.[48] It works by placing an enzyme in question in a test tube with AL and the cofactor NADPH, and then measuring how much NADPH is used over time.[49] Because AL and NADPH will not react in appreciable amounts to make DHIV without a KARI to catalyze the conversion, if NADPH use is detected, the enzyme in question is a KARI.[50] Because the Arfin assay tests use of NADPH, it provides no indication about a KARI's relative activity with use of NADH as the electron donor.[51]

By 1972, the "Enzyme Commission"—a body of experts organized "[t]o consider the classification and nomenclature of enzymes and coenzymes, their units of activity and standard methods of assay"[52]—created a specific "EC number 1.1.1.86" for KARI.[53] EC numbers catalog reactions that enzymes are capable of catalyzing.[54] Relying on KARI literature from the 1960s, including Arfin and Umbarger (1969), EC 1.1.1.86 depicts the KARI reaction as converting

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[47] *Id*.

[48] *Id*.; A04590-A04591, ¶28; A04637-A04638, ¶¶42-43.

[49] A04590-A04591, ¶28.

[50] *Id*.

[51] A04590-A04591, ¶28; A09149-A09150, ¶11.

[52] A04622-67, at A04628-A04632, ¶¶17-26.

[53] A04629, ¶20; A04635-A04636, ¶39; A04694.

[54] A04497-A04577, at A04502, ¶15; A04636-A04639, ¶¶39-46.

AL to DHIV using NADPH.[55] In the years that followed, references disclosed that KARIs also use the related cofactor NADH as an electron donor. For example, in 1991, a reference taught KARI enzymes from a genus of organisms called *Methanococcus* have "a broad specificity for NADPH and NADH…."[56] One such KARI is noted as being preferred in the Butamax Patents, and is expressly claimed by the '188 patent.[57] In 1997, another reference disclosed an *E. coli* KARI variant with higher "affinity" for NADH than NADPH.[58] By 2005, EC numbers were published online with hyperlinks to protein databases that provided full up-to-date information about the enzyme.[59] One leading database, BRENDA,[60] references that 1997 paper among others, and notes that for particular KARI enzymes having EC 1.1.1.86, NADH "can substitute for NADPH":[61]

[55] A04635-A04638, ¶¶39-43.

[56] A04893.

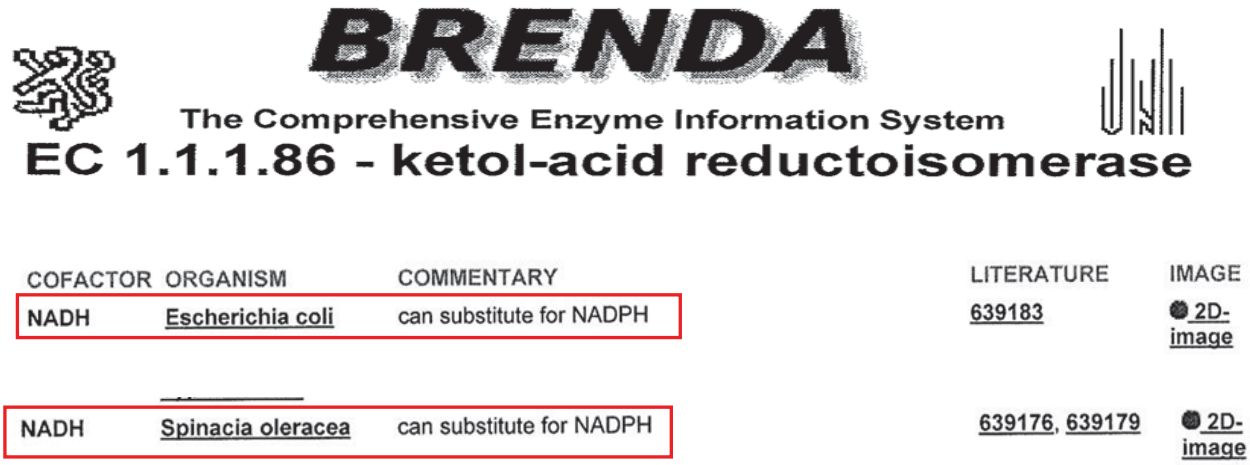
[57] A00152, 7:46-47; A00316, 336:32-35.

[58] A05205.

[59] A04506, n.3; A04630.

[60] BRENDA stands for BRaunschweig ENzyme DAtabase, and includes information regarding enzymes classified by the Enzyme Commission. A04632-A04633, ¶¶30-32.

[61] A16421; A16430 (excerpted and annotated in red); A04780; A04792; A04804.


BRENDA
The Comprehensive Enzyme Information System
EC 1.1.1.86 - ketol-acid reductoisomerase

COFACTOR	ORGANISM	COMMENTARY	LITERATURE	IMAGE
NADH	Escherichia coli	can substitute for NADPH	639183	2D-image
NADH	Spinacia oleracea	can substitute for NADPH	639176, 639179	2D-image

Thus, by 2005, based on the EC 1.1.1.86 listing, references, and BRENDA database, it was understood that KARIs may be identified by use of NADPH in the Arfin assay, but also may have substantial activity with NADH.

3. The Inventors Included the Entire Class of KARI Enzymes for Use in the Engineered Pathway

The Butamax Patents contain a detailed description of the invention "for the interpretation of the claims and the specification."[62] That description is consistent with KARI's plain meaning in 2005—first describing the reaction (AL to DHIV "using NADPH") set out in EC 1.1.1.86 and by which Arfin and Umbarger (1969) defined KARI activity, and then by citing resources to identify KARI sequences:

> [KARI] refer[s] to an enzyme that catalyzes the conversion of acetolactate to 2, 3-dihydroxyisovalerate using NADPH (reduced nicotinamide adenine dinucleotide phosphate) as an electron donor. Preferred

[62] A00152, 7:12-13.

> [KARIs] are known by the EC number 1.1.1.86 and sequences are available from a vast array of microorganisms, including, but not limited to, *Escherichia coli* … *Saccharomyces cerevisiae* … *Methanococcus maripaludis* … and *Bacillus subtilis* ...[63]

As of 2005, describing preferred KARIs as "known by EC 1.1.1.86" provided substantial sequence information, as databases disclosed a vast array of KARI sequences by that number.[64] It too provided functional information, as databases like BRENDA indicated KARIs having EC 1.1.1.86 could use NADH as a "substitute for NADPH." The specification provides further information by listing preferred sequences from diverse sources, including "*Escherichia coli*" "*Saccharomyces cerevisiae*," "*Methanococcus maripaludis*" and "*Bacillus subtilis*." These organisms comprise three different kingdoms of life,[65] and include KARIs like those from *Methanococcus*, which are reported and known to use NADPH and NADH in converting AL to DHIV.[66]

Example 2 parallels the detailed description of KARI by stating "[KARI] activity" is "measured using the method described by Arfin and

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[63] A00152, 7:35-50.

[64] *Supra* n.59.

[65] A10524, n.13; A05098, ¶¶51-52; A05100, ¶¶120-121.

[66] *Supra* n.56; *see also* A10566-A10567 (noting *S. cerevisiae* KARI uses NADH); A08780; A08794 (noting *S. cerevisiae* KARI has "promiscuous nucleotide specificity"); A05171, Table 44 (labeling *E. coli* KARI as "NAD(P)H").

Umbarger" (which uses NADPH).[67] In the working example, a KARI enzyme is reported as having a "specific activity" in the Arfin assay of 0.026 units/mg.[68] "Specific activity" in that assay is based on how much NADPH is used per minute, per milligram of KARI.[69] This assay identifies KARI enzymes by use of NADPH as electron donors. Gevo's expert admits this assay is the way the inventors told the world to identify KARI activity, stating "they did refer to that [Arfin and] Umbarger assay, so I would image that is enough for one to determine the activity, yes."[70] Because that assay uses NADPH, it does not rule out, determine, or evaluate whether an enzyme may also use NADH, or in what amount.[71] The Butamax Patents' working example lists KARI "activity" at 0.026 u/mg.[72] Thus, according to those patents, this must constitute "non-ancillary" KARI activity and any enzyme with roughly this activity would be considered a KARI.

4. The Butamax Inventors Prosecuted Claims to the Engineered Pathway Comprised of Entire Enzyme Classes

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[67] A00165, 33:45-47.

[68] A00168, 39:5-10.

[69] A04825; A10181, ¶66 ("The final value [for specific activity] is in the standard terms of enzyme units of μmol substrate converted to product per minute per mg enzyme.").

[70] A09416, 235:20-236:6.

[71] *Supra* n.51.

[72] A00168, 5-9.

During prosecution, the inventors sought to claim the engineered pathway based on entire enzyme classes. By referring the Examiner to the disclosures in the specification of representative sequences, EC numbers, standard assays, and other references, they obtained such claims.

a. The '188 Patent File History

Original claim 1 of the '188 patent recited five substrate-to-product conversions of the engineered pathway, such as AL to DHIV at step b, without reciting the class of enzyme used.[73] The Examiner rejected this claim for lack of written description and enablement.[74] The inventors disagreed and provided a webpage printout of EC numbering, which notes enzymes are classified "according to the reaction they catalyze."[75] The inventors amended claim 1 to identify the enzyme class used at each step (including KARI for step b) and "limit[ed] the enzyme terms to their corresponding EC numbers."[76]

The Examiner withdrew the written description rejection, but maintained the non-enabled rejection.[77] To provide further evidence that a POSA could make and use the claimed invention, the inventors cited the BRENDA

[73] A06906.

[74] A06923-A06925.

[75] A07058.

[76] A07093.

[77] A07117.

database, and stated that it, along with other protein databases, "provide direct links to exact structural definitions" of the claimed enzyme classes.[78] The inventors also referenced the specification's "4 examples of polypeptides having [KARI] activity, all having EC number 1.1.1.86."[79] These sequences include those mentioned above that use both cofactors. After an amendment delineating the class of enzymes used at each step, the Examiner withdrew the rejection.[80]

b. The '889 Patent File History

The inventors initially presented an independent claim of the '889 patent application also reciting the engineered pathway without the class of enzymes used.[81] The Examiner rejected this claim for no written description.[82] Opposing the rejection, the inventors amended the claims to recite specific classes of enzyme by name (*e.g.*, KARI at step (b)).[83] They cited the specific enzyme sequences disclosed in the specification (including the KARIs noted above),[84] and specifically relied on assays disclosed in the specification to identify each class of enzyme, stating: "[T]he Examples describe … the methods of assaying the

[78] A07143.

[79] *Id.*

[80] A07209; A07251.

[81] A07541.

[82] A07570-A07571.

[83] A07582.

[84] *Id.*

respective enzyme's activity. For illustration purposes…*Example 2 provides this information for* [*KARI*]"[85] (referring to the Arfin assay mentioned above). The Examiner then withdrew that rejection.[86]

5. The Butamax Patents Claim the Engineered Pathway Comprised of Entire Enzyme Classes

The '188 patent claims a recombinant host cell that produces isobutanol via the engineered biosynthetic pathway. Claim 1 recites each class of enzyme that catalyzes the substrate-to-product conversions by name, and EC number.[87] Dependent claim 15 recites the specific preferred KARI sequences of *Methanococcus* (known to substantially use NADPH and NADH), among other KARI sequences that use NADH.[88] Claim 21 is directed to isobutanol production under anaerobic conditions (where NADH is more abundant than NADPH for use by KARI).[89]

The '889 patent claims recite a method for producing isobutanol by recombinant yeast expressing the engineered pathway.[90] Unlike claim 1 of the '188 patent, the '889 patent recites each class of enzyme by name only, and not EC

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[85] A07583 (emphasis added).

[86] A07594.

[87] A00316.

[88] *Id.*

[89] *Id.*; *supra* n.36.

[90] A00487.

numbers.[91] Like the '188 patent, the '889 patent also recites producing isobutanol under anaerobic conditions. The '889 patent includes dependent claim 14, which recites "one or more enzymes of the said engineered … pathway uses NADH as an electron donor,"[92] which must include KARI, as one of only two pathway enzymes that use NADH.[93]

II. Gevo's Infringement of Butamax's Patented Technology

The same year DuPont filed its patent applications, Gevo was formed under the name Methanotech with a goal of making methanol, *not* isobutanol.[94] Only after that failed, and DuPont announced it was pursuing biobutanol in 2006, did Gevo switch its name from Methanotech and its target to isobutanol.[95] Gevo admits to being aware of Butamax's patents while going forward with its product, and its documents show it relied on Butamax's patented technology to do so.[96] Prior to being sued, Gevo reported to the Environmental Protection Agency ("EPA") that it uses an engineered pathway with the same class of enzymes, and EC numbers disclosed and claimed by the Butamax Patents.[97] Gevo also applied

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[91] *Id*.

[92] A00487, 326:37-40.

[93] A04603-A04604, ¶53.

[94] A10456-A10457, ¶¶34-35.

[95] *Id*.

[96] A04116, 62:15-65:23; A01303-A01305, ¶¶54-56.

[97] A09804.

for a patent application citing the Butamax Patents' corresponding PCT application as an embodiment of Gevo's application.[98]

> In one embodiment, a yeast microorganism is engineered to convert a carbon source, such as glucose, to pyruvate by glycolysis and the pyruvate is converted to isobutanol via an engineered isobutanol pathway (PCT/US2006/041602, PCT/US2008/053514). Alternative pathways for the production of

After learning of Gevo's infringement, Butamax sued Gevo on 19 claims of the '188 patent, and 18 claims of the '889 patent.[99] Gevo submitted an interrogatory response and expert reports contesting *only* that its products do not meet the KARI element.[100]

A. Gevo Uses a KARI Covered by the Butamax Patents

Gevo has developed microorganisms for commercial isobutanol production that express KARI enzymes for the conversion of AL to DHIV. Gevo refers to the two different KARI enzymes it uses as P2D1A1 and SE26E6.[101] These enzymes use NADPH in the Arfin assay, having more "units" of activity than a working KARI example in the Butamax Patents.[102] While Gevo denies they

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[98] A10959; A11003, 18:30-55; A01303-A01305, ¶¶54-56.

[99] A16896.

[100] A09694-97; A09642-A09643; A09647-A09648.

[101] A00037, n.17.

[102] P2D1A1 has activity with NADPH at 0.15 U/mg, and SE26E6 at 0.1 U/mg, while the Butamax Patents report KARI activity of 0.026 U/mg. *Compare* A09868, Table 34 (indicating P2D1A1's specific activity for NADPH is 0.15 U/mg), *and*

are KARIs of the claimed invention, prior to being sued, Gevo regularly referred to them in same manner as the Butamax Patents: *as a KARI, having EC 1.1.1.86*[103]:

[redacted]

In 2009, Gevo reported to the EPA its use of a "KARI; EC 1.1.1.86," while noting its KARI "utilizes" NADH.[104] The head of Gevo's biocatalyst group, Dr. Asleson, testifying as a Gevo corporate witness, stated this "would have been the best way [Gevo's scientist] knew how to describe that enzyme."[105]

After this litigation, Gevo made up a new name for its KARIs—"NKR"—in a clear attempt to avoid admitting infringement.[106] Gevo did so apparently unaware of its internal memos on file. For example, [redacted]

A09873-A09873, Table 49 (indicating SE26E6's specific activity for NADPH is 0.1 U/mg), *with* A00168, 39:5-10 (reporting KARI "activity of 0.026 units/mg").

[103] A04198 (excerpted and highlighting added); A10574.

[104] A09804; *see also* A09692.

[105] A09675, 202-205; A10195-97; A10208-209.

[106] Gevo's former Executive Vice President of Technology, Dr. Glassner, admitted that Gevo itself described its KARI enzyme by the same EC number in the Butamax Patents, and that Gevo only decided to stop calling its enzymes KARIs on advice of counsel "since this litigation started." A04450-A04452.

[redacted]

Putting these name changes aside, Gevo's own non-infringement expert has admitted that Gevo's enzymes "meet the definition" of KARI.[108]

Given this evidence, Gevo then raised a different non-infringement argument that, although KARIs, Gevo's enzymes do not infringe because they are "NADH-dependent." However, Gevo's patent applications,[109] and admissions[110] indicate its KARIs catalyze AL to DHIV, and the evidence shows they are virtually

[107] A09680 (emphasis original, highlighting added).

[108] A04365, 185.

[109] A09732, ¶84; A09871, ¶17.

[110] A09694-A09697; A09631, 369-371; A09851; A09887, 100:16-25; A09890, 116:23-117:22.

identical to a preferred KARI sequences listed in the Butamax Patents (>98% identical),[111] and to others having EC 1.1.1.86 (99% identical).[112] Gevo itself tested its KARIs in an Arfin assay, showing they use NADPH catalyzing AL to DHIV as described in the Butamax Patents.[113] Gevo's KARIs have activity with NADPH roughly equal to activity of other published "KARIs collected in the BRENDA database"[114]—the same database the Butamax inventors relied on during the prosecution history as disclosing enzymes of the claimed inventions.[115] [redacted]

[redacted]

[111] A04375-A04376, 222-227; A09817, ¶¶156-57; A09830-A09831; A09730-A09731, ¶¶80-81; A09757-A09758 (showing P2D1A1 is 99% identical to the E. coli KARI having EC number 1.1.1.86); A09855-A09856, ¶¶36-38.

[112] A09817, ¶¶158-59, A09833-A09834; A09730-A09731, ¶¶80-81; A09760-A09761 (showing the same for SE26E6); A09857-A09858, ¶¶38-41.

[113] *Supra* n.102.

[114] *Compare* A09868, Table 34 (noting P2D1A1's specific activity for NADPH is 0.15 U/mg), *with* A10181, ¶64 (noting BRENDA discloses KARIs having activity of 0.15 U/mg); *see also* A09895.

[115] A07143.

[116] A04226 (highlighting and annotations added); A04368, 194-197. [redacted] A04217.

Butamax's testing expert also assayed Gevo's KARIs in the Arfin assay, and confirmed that they have statistically significant activity with NADPH.[117]

Thus, these Gevo pre-litigation documents, admissions, and other evidence show that Gevo's enzymes are KARIs according to the Butamax Patents.

III. The District Court's Claim Construction and Summary Judgment Opinion

During the first appeal, this Court directed the district court to "reconsider its construction" of KARI. Nonetheless, the district court construed KARI in substantially the same manner as before, ruling it means an enzyme that is "NADPH-dependent."[118] The court declined to adopt KARI's plain meaning or the

[117] A09897-A09899.

[118] A00022. At the pretrial hearing, the court confirmed that while it dropped the term "solely" from its initial construction, it continued to construe the KARI element as limited only to "NADPH-dependent" KARIs, excluding enzymes that are "NADH-dependent" or dual dependent. A10831, 11:4-12.

description in the specification,[119] and rejected the Arfin assay as the tool to identify KARI, despite that test being expressly stated in the Butamax Patents, and confirmed by the prosecution history.[120] Then, after reviewing extensive amounts of extrinsic evidence, the court concluded it could not "find a quantification" for its own construction in the parties' documents and decided to "leave[] the explanation" of the "dependent" term to the parties' scientific experts at trial.[121]

On infringement, the district court made clear it found a disavowal of claim scope of any KARI having more than ancillary activity with NADH (*i.e.*, NADH-dependent enzymes). This is evident because court ruled there was an issue of fact as to "how a person of ordinary skill in the art at the time the invention was made would determine *NADH*-dependency,"[122] rather than whether Butamax could prove that Gevo's KARIs are *NADPH*-dependent. Stated differently, the court required Butamax to disprove Gevo's KARI's are NADH-dependent, as opposed to prove they are NADPH-dependent. Because the court rejected construing KARI according to its plain meaning, and rejected defining

[119] A00021.

[120] *Id*.

[121] A00040, n.25.

[122] A00040 (emphasis added).

KARI based on activity in the Arfin assay, Butamax stipulated to no literal infringement.[123]

Next, the court found "no plausible doctrine of equivalents argument" because NADH and NADPH cannot be viewed as insubstantially different[124]—a basis Gevo did not move on, and which does not concern an element of the claimed invention. Yet, the court did not even address whether Gevo's KARIs are equivalent to a "NADPH-dependent KARI" in context of the claimed invention, much less draw all reasonable inferences in favor of Butamax, which submitted substantial evidence on that issue.

On validity, the court determined that claims 12 and 13 of the '889 patent were invalid for lack of written description, also without crediting the substantial evidence from Butamax's and Gevo's own experts from which a reasonable jury could find otherwise.[125] And, going beyond the briefing again, the court's order stated these claims were invalid for lack of enablement, although Gevo did not move on this basis and the court's opinion did not address this issue.[126]

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[123] A10770-A10772.

[124] A00041.

[125] A00054-A00055.

[126] A00059.

SUMMARY OF ARGUMENT

The entire literal infringement issue before this Court turns on the proper claim construction of "acetohydroxy acid isomeroreductase having the EC number 1.1.1.86" of the '188 patent and "acetohydroxy acid isomeroreductase" of the '889 patent. Following the well-settled canons of claim construction, construing the KARI element according to its plain meaning, in light of the patents' intrinsic evidence, there is no question that Gevo literally infringes.

The district court, however, denied Butamax's request for summary judgment of literal infringement based on its construction of KARI as "NADPH-dependent." The court's analysis premised on that erroneous construction cannot withstand scrutiny, and this Court should reverse.

First, the court's narrow construction of the KARI element as "NADPH-dependent" is erroneous. It limits the plain meaning—which is not defined by cofactor "dependency"—and is contrary to the specification's express description of KARI enzymes. The court's construction turns a clear description of "using NADPH" into a vague term, "NADPH-dependent." The specification did not redefine KARI more narrowly than KARI's plain meaning, or disavow any subcategory of KARI enzymes. It merely refers to the manner used to identify a KARI: the Arfin assay. The court, however, misinterpreted that description to require KARI to have "dependency" on one cofactor over another, turning the

KARI element—a compound—into a vague process element, which the court itself could not define. To the extent the inventors can be considered to have acted as their own lexicographer, their express description must apply, not the court's rewrite of that phrase, which imports a negative limitation found nowhere in the claims or specification with respect to KARI. Indeed, Gevo infringes because it indisputably uses KARIs that catalyze the AL to DHIV conversion recited by the claims, have virtually identical sequences with KARIs disclosed in the patents, and have KARI activity in the Arfin assay.

Second, the court erred in finding no plausible DOE argument based on the purported "not insubstantial" difference of NADH and NADPH. Gevo did not move for no DOE on this basis, and the court failed to address the proper legal test, *i.e.*, whether Gevo's KARIs are equivalent to the KARI element as construed, and in context of the claimed invention. On that issue, Butamax proffered substantial evidence from which a reasonable jury may return a verdict of DOE infringement.

Third, the court erred in ruling claims 12 and 13 of the '889 patent are invalid for lack of written description. The court did not credit Butamax's evidence, including Gevo's expert's admission that the specification described the claimed invention "completely." Butamax provided substantial evidence from which a reasonable jury could rule these claims are not invalid. Similarly, the

court clearly erred by ordering these claims invalid for lack of enablement without briefing, notice, or discussion of this issue in its opinion.

When these errors are rectified, this Court should enter judgment that Gevo literally infringes the Butamax Patents,[127] and reverse the invalidity of claims 12 and 13, and remand for further proceedings.

STANDARD OF REVIEW

Claim construction is an issue of law, reviewed *de novo*.[128] This Court reviews "the grant or denial of summary judgment applying the law of the relevant regional circuit."[129] In the Third Circuit, review of a grant or denial of summary judgment is plenary.[130] On summary judgment, the Court credits all of the non-movant's evidence and draws all justifiable inferences in its favor.[131]

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[127] *See, e.g.*, *Magnivision, Inc. v. Bonneau Co.*, 250 F.3d 758, at *11 (Fed. Cir. 2000) (reversing claim construction, and entering judgment of infringement).

[128] *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 981 (Fed. Cir. 1995) (*en banc*); *see Cybor Corp. v. FAS Tech., Inc.*, 138 F.3d 1448, 1456 (Fed. Cir. 1998) (*en banc*); *but see Lighting Ballast Control LLC v. Philips Elec. N. Am. Corp*., 500 Fed App'x 951, 952 (Fed. Cir. 2013).

[129] *CLS Bank Int'l v. Alice Corp. Pty. Ltd.*, --F.3d--, 2011-1301, 2013 WL 1920941 at *3 (Fed. Cir. May 10, 2013) (*en banc*).

[130] *Giles v. Kearney*, 571 F.3d 318, 322 (3d Cir. 2009).

[131] *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255 (1986).

ARGUMENT

IV. The District Court Erred in Construing the KARI Element

The district court erred by narrowly construing the KARI element as "NADPH-dependent," contrary to its plain meaning and the description provided in the Butamax Patents. Based on the intrinsic evidence, KARI should be given its plain meaning, encompassing any enzyme having KARI structure, with activity in the Arfin assay. The court also erred by construing the KARI of the '889 patent to mean "having EC 1.1.1.86," although this term does not appear in those claims.[132]

A. The Plain Meaning of KARI Is an Enzyme Structurally Similar to Known KARIs and that Catalyzes the AL to DHIV Conversion

A claim term is generally given its "ordinary and customary meaning," that is, "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention."[133] There is a "heavy presumption" that this meaning applies, unless it can be shown that "the patentee *expressly* relinquished claim scope."[134] That did not occur here.

In 2005, the time of the Butamax invention, the plain meaning of KARI was an enzyme that catalyzes the conversion of AL to DHIV. Indeed, Gevo

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[132] *MBO Labs. Inc. v. Becton, Dickinson & Co.*, 474 F.3d 1323, 1333 (Fed. Cir. 2007) ("grafting" limitation from one claim to another is error).

[133] *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (*en banc*)..

[134] *Epistar Corp. v. Int'l Trade Comm'n*, 566 F.3d 1321, 1334 (Fed. Cir. 2009) (emphasis added).

does not dispute that KARI's plain meaning does not specify cofactor dependency, and that KARIs have the ability to catalyze that conversion with either cofactor.[135] In 2005, KARI enzymes were identifiable by structural similarity to known KARIs, and by testing positive in a recognized assay. Thus, the inventors included in their application a diverse set of representative sequences, and the manner of identifying KARI activity (a positive test in the Arfin assay). They confirmed these bases define KARI in the prosecution history, citing to the Examiner those sequences, EC number 1.1.1.86, and the Arfin assay.

Moreover, while that Arfin assay uses NADPH as the electron donor, references disclosed certain KARI enzymes, such as from *Methanococcus*, have substantial (non-ancillary) activity with either cofactor,[136] and BRENDA disclosed KARIs that can use NADH as a substitute for NADPH.[137] In turn, the inventors claimed a *Methanococcus* KARI, and cited the BRENDA database during the prosecution history. Thus, the Butamax Patents' intrinsic evidence confirms the inventors covered the KARI class as a whole. Following the well-settled canons of construction in *Phillips*, analyzing that intrinsic evidence, it is clear that KARI

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[135] A10240-A10241 (Gevo stating the plain meaning of KARI is: "A naturally-occurring or engineered enzyme that catalyzes the reaction of [AL to DHIV] using NADH or NADPH as a cofactor").

[136] *Supra* n.56.

[137] *Supra* n.61. It is understood that all KARIs, whether labeled as NADH or not, will be able to use NADPH. A04594-95.

should be construed according to its plain meaning, and not limited to "NADPH-dependent" enzymes.[138]

1. The Claims Confirm KARI Should Be Given Its Plain Meaning

Claim construction begins with the claim language itself.[139] Here, the independent claims dictate that the KARI element should cover the entire class.

Independent claim 1 of the Butamax Patents recites KARI as catalyzing the conversion of AL to DHIV, thereby expressly covering the entire class of KARIs that can be used at step (b) of the engineered pathway.[140] Nothing in those claims indicates KARI should be limited to "NADPH-dependent" enzymes—they do not recite cofactors or "dependency." As this Court has noted: "The danger of improperly importing a limitation is even greater when the purported limitation is based upon a term not appearing in the claim."[141]

Indeed, it would be illogical and contrary to the purpose of invention to exclude KARIs that are "NADH-dependent" or have "non-ancillary" activity

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[138] *Phillips*, 415 F.3d at 1316.

[139] *Id*. at 1313-14.

[140] A00316; A00487.

[141] *Amgen Inc. v. Hoechst Marion Rousell, Inc*., 314 F.3d 1313, 1325 (Fed. Cir. 2003).

with NADH because such KARIs are useful in the claimed engineered pathway.[142] Butamax sought claims in the initial application directed to producing isobutanol during anaerobic conditions,[143] and obtained them in the '188 and '889 patents (claims 21 and 2, respectively).[144] Under those conditions, which the Butamax Patents describe as "preferred,"[145] NADH is known to be more abundant than NADPH.[146] Thus, the inventors wanted and *included* KARIs that use NADH, rather than exclude such enzymes.[147]

Further, the Examiner did not understand the specification to exclude such KARIs because the Examiner allowed dependent claims covering KARI enzymes that use NADH. Such claims are rendered meaningless by an NADPH-dependent construction, contrary to settled Federal Circuit law.[148] Claim 14 of the

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[142] *See, e.g.*, *Medegen MMS, Inc. v. ICU Med., Inc.*, 317 Fed. App'x 982, 986 (Fed. Cir. 2008) (reversing claim construction noting that the limitation imposed is not "central to the invention itself").

[143] *E.g.*, A05881, draft claim 44.

[144] A04596, ¶39.

[145] A00160, 24:22-25.

[146] A04596, ¶39.

[147] *Hoechst Celanese Corp. v. BP Chems. Ltd.*, 78 F.3d 1575, 1581 (Fed. Cir. 1996) ("[I]t is unlikely that an inventor would define the invention in a way that excluded the preferred embodiment, or that persons of skill in this field would read the specification in such a way.").

[148] *See, e.g.*, *CytoLogix Corp. v. Ventana Med. Sys., Inc.*, 424 F.3d 1168, 1173 (Fed. Cir. 2005); *Wright Med. Tech., Inc. v. Osteonics Corp.*, 122 F.3d 1440, 1445 (Fed. Cir. 1997).

'889 patent recites "one *or more*" enzymes in the claimed pathway "use NADH as an electron donor." KARI is one of only two enzymes that can do so.[149] Thus, for the "or more" limitation to make sense, KARI must be construed to permit use of NADH.[150]

Notwithstanding this conflict, the district court stated claim 14 was of "no moment" because other enzymes of "the claimed pathway were defined by the patentees as using NADH as an electron donor."[151] However, "that is not a coherent reading of the specification,"[152] because the court relied on the specification's description of other enzymes that are ***not*** part of the claimed pathway.[153] Indeed, Gevo's expert and Gevo itself concede that KARI is one of

[149] A04603-A04604, ¶53.

[150] The district court interpreted the specification's description of KARI as "using NADPH" to mean "dependent." A00020, n.14. If "use" in claim 14 is interpreted consistently, however, it means claim 14 covers NADH-dependent KARIs. Thus, the only way to reconcile claim 14 and the specification is if "using NADPH" does not exclude enzymes that also may use NADH. Indeed, Chief Judge Rader previously questioned whether claim 14 "cut against" Gevo's construction, stating if step 2 is construed as "only using NADPH as the electron donor, then the term 'or more' would be [read] out" of claim 14. A09554, 24:15-18.

[151] A00021.

[152] *Cf. ArcelorMittal France v. AK Steel Corp.*, 700 F.3d 1314, 1320-21 (Fed. Cir. 2012) (reversing-in-part a construction based on misreading the specification).

[153] A00021 (citing A00327, 7:54-56, 7:67-8:1, 8:19, 8:51, including "branch-chain keto acid dehydrogenase", "acylating aldehyde deydrogenase," and "valine dehydrogenase," which are *not* a part of the claimed pathway).

only two enzymes in the claimed pathway that can use NADH.[154] Thus, the district court committed clear error by misreading the specification.

The construction also reads out the preferred KARI sequence from *Methanococcus* expressly recited by claim 15 of the '188 patent, which is not NADPH-dependent, and has substantial activity with both cofactors. The district court did not even address claim 15, but stated the evidence of *Methanococcus's* significant use of NADH comes only from "a single reference," Xing (1990), lacking data.[155] However, Xing (1990) is a peer reviewed publication, which states *methanococcal* KARIs have "broad specificity for NADPH and NADH."[156] Gevo itself cited that reference in its patent application, stating "a KARI from *Methanococcus* species can be used [in an engineered pathway]," and referring to this enzyme as "NADH-utilizing."[157] [redacted]

[redacted]

[154] A09640 at 451:3-25; A10554 at 482:21-483:5; A10101.

[155] A00019-A00020.

[156] A04893.

[157] A15841, ¶82.

[158] A10560-A10561, 264-267; A10551.

[redacted] By excluding KARIs that are NADH-dependent or dual dependent, the court's construction excludes this expressly claimed sequence. Because a court "must not interpret an independent claim in a way that is inconsistent with a claim which depends from it," the narrow NADPH-dependent construction, which renders claim 15 meaningless, should be reversed.[160]

Because this construction nullifies multiple dependent claims, it creates a strong presumption the construction is improper,[161] which can be overcome only where a contrary construction is "dictated" by the written description or prosecution history.[162] However, as show below, these resources compel defining KARI by its plain meaning.

2. The Specification's Figure and Detail Description Confirm KARI Should Be Given Its Plain Meaning

The specification confirms that the Butamax Patents cover the entire class of KARI enzymes capable of converting AL to DHIV. Figure 1 discloses KARI's function, indicating any electron source may be used for the reduction (be it NADH or NADPH).[163]

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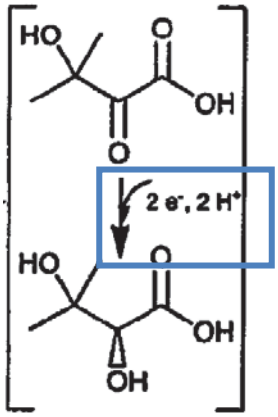
[159] A09645, 505:7-24; A09646, 508:7-509:16.

[160] *See, e.g.*, *Wright*, 122 F.3d at 1445; *accord MBO*, 474 F.3d at 1333 (excluding a preferred embodiment is "rarely, if ever, correct").

[161] *See Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 910 (Fed. Cir. 2004).

[162] *Seachange Int'l, Inc. v. C-Cor, Inc.*, 413 F.3d 1361, 1369, 1370-72 (Fed. Cir. 2005).

[163] A00148 (annotation added).



This Figure matches the "preferred" engineered pathway in the specification,[164] and pathway expressly claimed,[165] neither of which discuss cofactors or "dependency."

The detailed description also depicts KARI consistently with its plain meaning, stating it "catalyzes the conversion of [AL] to [DHIV] using NADPH … as an electron donor."[166] This sentence describes KARI the way it had been identified in the seminal, "gold standard," Arfin assay[167] and as described in EC 1.1.1.86.[168] The inventors certainly were not intending this to redefine KARI to exclude enzymes with this activity, which also have activity with NADH, as interpreted by the court. Indeed, that reading contradicts patent rules of interpretation. This Court "has repeatedly emphasized that an indefinite article 'a'

[164] A00154, 12:5-18.

[165] A00316; A00487.

[166] A00152, 7:35-40.

[167] A10559, 239:14-21.

[168] A04778.

or 'an' in patent parlance carries the meaning of '*one or more*' in open-ended claims containing the transitional phrase 'comprising.' That 'a' or 'an' can mean 'one or more' *is best described as a rule, rather than merely as a presumption or even a convention*."[169] The court's construction violates this well settled rule by interpreting "using NADPH ... as an electron donor" to mean "dependent" on that donor to the exclusion of using NADH.

The remainder of KARI's detailed description also contradicts the court's construction. By stating "[p]referred" KARIs "are known by EC 1.1.1.86," the inventors used to the typical way all KARIs were described in 2005.[170] Indeed, prior to this litigation, *Gevo* understood EC 1.1.1.86 to be the "best way" to refer to a KARI that "utilizes" NADH.[171] Such KARIs react using NADPH in the Arfin assay, and are listed under EC 1.1.1.86 in the BRENDA database.[172] Thus, such KARIs are encompassed by the Butamax Patents, which include KARIs known by that number.

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[169] *Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1342 (Fed. Cir. 2008) (emphasis added). Both independent claims of the Butamax Patents recite the substrate-to-product conversions using the open-ended term "comprising." A00316; A00487.

[170] A4633-35, ¶¶33-38; A4503-05, ¶¶18-24; A09161-72, at A09167, ¶14.

[171] *Supra* n.105; A09692.

[172] *Supra* n.61.

The detailed description also lists preferred KARIs from three different kingdoms of life including enzymes that can use either cofactor, further showing Butamax covered all KARIs.[173]

3. The Examples Use the Arfin Assay to Test KARI Activity, Consistent with KARI's Plain Meaning

Example 2 dovetails with the specification's description of KARI by citing the Arfin assay. That seminal reference teaches the test to identify if an enzyme is a KARI—whether there is activity in the assay. As such, this test should be employed to determine whether an enzyme meets the KARI element. This Court has regularly upheld this practice, noting that where a specification identifies a test and "unmistakably instructs one of skill in the art" to conduct that test to determine a particular claim element, that test is sufficient to determine whether the element is met.[174]

Indeed, Gevo's expert agreed the Butamax inventors "did refer to that Umbarger assay, so I would imagine that *that is enough for one to determine the activity, yes*."[175] And Gevo itself has admitted this assay "does not show co-factor

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[173] *Supra* n.56, n.66, n.157, n.158, n.159.

[174] *Invitrogen Corp. v. Clontech Labs. Inc.*, 429 F.3d 1053, 1077 (Fed. Cir. 2005); *see also Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1367 (Fed. Cir. 2011).

[175] A09416, 235:20-236:6.

dependencies."[176] Thus, Butamax did not limit KARI to one cofactor-dependent subset—the claimed engineered pathway does not make such distinctions. KARI is a chemical compound, not a method step or cofactor. *Any* enzyme with appropriate structure that catalyzes AL to DHIV using NADPH in the Arfin assay is a KARI, and does not stop being so if, when placed in different assay or test, it may also use NADH.[177] By construing KARI based on cofactor dependency, this element directed to a chemical compound morphs into a process element—a result repeatedly rejected by this Court.[178]

4. The Court Misunderstood the Purpose of the Specification's Description of the Enzymes

The district court misunderstood the purpose of the specification's description of the different enzyme classes, which describes KARI as "using NADPH," and other non-KARI enzymes as using "NADH … and/or NADPH."[179] The court assumed that by describing KARI as using NADPH, Butamax implicitly excluded KARIs that are "NADH-dependent" or "dual dependent."[180]

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[176] A08759, n.11, *accord* A09144-60, at A09149-A09150, ¶11.

[177] *SRI Int'l v. Matsushita Elec. Corp. of America*, 775 F.2d 1107, 1122 (Fed. Cir. 1985) ("[The law] does not require that an applicant describe in his specification every conceivable and possible future embodiment of his invention.").

[178] *See, e.g.*, *3M Innovative Props. Co. v. Avery Dennison Corp.*, 350 F.3d 1365, 1371-72 (Fed. Cir. 2003); *Amgen*, 314 F.3d at 1329.

[179] A00014.

[180] A00021, n.15.

These different descriptions, however, are "amenable to a second (and more reasonable) interpretation."[181] By stating KARI catalyzes the AL to DHIV conversion using NADPH, Butamax did not exclude KARIs that also catalyzed that conversion using NADH. Rather, in 2005, when these applications were drafted, several other enzyme classes described in the specification had multiple EC numbers, reciting different reactions, including using NADH, or NADPH, or both.[182] There were also different tests or assays for identifying those enzyme classes disclosed by their various EC numbers.[183] On the other hand, in 2005 and today, KARI has only one EC number (1.1.1.86). It lists the reaction as using NADPH because that number is based on Arfin and Umbarger (1969), which describes the standard assay for KARI as *detecting* use of NADPH during the conversion of AL to DHIV.[184] In 2005, KARI was not broken down by EC number into three different categories, and the specification's description of "using NADPH" should not be read to constitute an express disavowal of KARIs that also

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[181] *Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1371 (Fed. Cir. 2005) (rejecting disavowal based on more reasonable explanation of specification).

[182] For example, the specification describes "branched-chain alcohol dehydrogenase" enzymes as using NADH and/or NADPH, but lists three separate EC numbers for those enzymes—EC 1.1.1.1, EC 1.1.1.2 and EC 1.1.1.265. A00152, 8:9-24.

[183] A04513-A0518; A04643-A04651.

[184] A04635-A04639, ¶¶39-44; A04506-A04508, ¶¶27-29.

have non-ancillary use with NADH. Indeed, those KARIs also test positive in the Arfin assay, and are listed under EC 1.1.1.86 by BRENDA.[185]

The court's opinion improperly construed the description of KARI based on non-KARI enzymes disclosed in the specification, but "ignore[d] the distinct contexts in which these terms are used."[186] Because Butamax described each enzyme class based on the corresponding EC numbers, and standard assays, it does not evince "a clear intention to limit the claim scope" to exclude any subcategory of KARI.[187] As named inventor Dr. Maggio-Hall testified, "we didn't mean[] to exclude any KARI enzyme. The important part [for KARI] was the acetolactate being converted to the next step in our pathway."[188] Indeed, as this Court stated in a similar case where a defendant sought to impose a negative limitation on a claim to avoid infringement, the "point is not whether the specification suggests the use" of an additional feature—like use of cofactors other

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[185] A04780; A04792; A04893.

[186] *Aventis Pharms. Inc. v. Amino Chems. Ltd.*, --F.3d--, 2011-1335, 2013 WL 2151105, at *8-9 (Fed. Cir. May 20, 2013) (reversing construction where "district court imposed a single interpretation even though th[e] context requires separate definitions").

[187] *See, e.g.*, *Thorner v. Sony Computer Entm't Am. LLC*, 669 F.3d 1362, 1368 (Fed. Cir. 2012) ("[T]he 'implied' redefinition must be so clear that it equates to an explicit one."); *Martek Biosciences v. Nutrinova*, 579 F.3d 1363, 1381 n.6 (Fed. Cir. 2009).

[188] A09423, 229:12-20; *see, e.g.*, *On-Line Techs. v. Bodenseewerk Perkin-Elmer GmbH*, 386 F.3d 1133, 1140 (Fed. Cir. 2004) (relying in-part on inventor testimony to rebut narrow construction and use of extrinsic evidence).

than NADPH here—but rather "whether the claim and specification in effect preclude [use of] any additional [feature] or otherwise require that the claim be limited… [to] *only* the structures of embodiments specifically described in the specification."[189] Here, nothing in the intrinsic evidence indicates that KARI must be limited to "dependency" on NADPH, *but not* NADH. And, employing a KARI in the engineered pathway having an additional feature of using NADH does not take that enzyme beyond the purview of the claims.[190]

Indeed, if one were to look to the patents' description of other enzymes to imply a meaning for KARI, it shows Butamax did ***not*** redefine KARI as NADPH-dependent because the specification expressly describes other enzymes as "NADPH-dependent," but *never does so for KARI*.[191] As noted above, the Butamax Patents cover the full scope of KARIs.

5. The Prosecution History Confirms the KARI Element Should Be Given Its Plain Meaning

During the prosecution histories, the inventors cited references, and portions of the specification that clearly indicate the claims cover use of the entire

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[189] *Stitfung v. Renishaw PLC*, 945 F.2d 1173, 1178 (Fed. Cir. 1991) (emphasis in original).

[190] *Omega Eng'g, Inc, v. Raytek Corp.*, 334 F.3d 1314, 1323 (Fed. Cir. 2003) (reversing construction of "negative limitation," where patent lacked express intent to confer such a meaning); *Stitfung*, 945 F.2d at 1178 (reversing construction precluding claimed structure from having additional features).

[191] A00150, 4:60-63; A00154, 12:58-60; A00168, 40:34-39.

class of KARIs. Importantly, the district court erroneously disregarded the '889 prosecution history altogether,[192] where the inventors expressly noted KARI was identified by activity in the Arfin assay—never by "NADPH-dependency," or lack of "NADH-dependency."[193]

During the '188 patent prosecution, the Examiner issued several 112 rejections. Rather than narrowing the claims to any subset of KARIs, the inventors amended the claims to recite KARI having EC 1.1.1.86, and cited the BRENDA database, and preferred KARI sequences from the specification.[194] These resources disclose a panoply of KARI sequences and functions (including KARIs that use NADH and NADPH), providing a "clear indication" that the KARI term is used "in a manner broad enough to encompass" the entire class.[195]

During the '889 patent prosecution, the inventors were confronted with similar rejections and traversed them by pointing to the preferred KARI sequences, and by identifying KARI activity based on the Arfin assay.[196] Thus, the inventors placed the world on notice that if an enzyme sequence is similar to those

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[192] A00012, n.5 (limiting discussion to the prosecution history of the '188 patent, erroneously stating the file histories of the two patents "substantially track each other").

[193] A07583.

[194] *Supra,* sect. I.A.4.a.

[195] *See*, *e.g.*, *Martek*, 579 F.3d at 1377.

[196] A07583.

disclosed, and has activity in the Arfin assay, it is covered by the claimed invention. Because there were no prior art rejections made concerning cofactor dependency, and the inventors did not consider cofactor dependency to be an element of their invention, they were "free to draft … broadly," without limitation to any cofactor dependency.[197] Stated simply, because there was no reason or requirement to exclude "NADH-dependent" KARIs, they were not excluded.

B. The District Court Misapplied the Lexicography Exception

Butamax did not redefine KARI inconsistently with its plain meaning, nor disavow any subset of KARIs, but merely described the typical way to test for KARI activity. However, to the extent the description could be read as unique or special lexicography, the district court erred by not adopting it and by changing "using NADPH" to "NADPH-dependent."[198] By rejecting the express description and importing a negative limitation excluding KARIs that also have non-ancillary activity using NADH, the court legally erred.

1. The Court Erred in Narrowing the KARI Element Contrary to the Express Written Description

"A patentee may act as its own lexicographer and assign to a term a unique definition that is different from its ordinary and customary meaning;

[197] *Ethicon Endo-Surgery, Inc. v. U.S. Surgical Corp.*, 93 F.3d 1572, 1582 n.7 (Fed. Cir. 1996).

[198] Indeed, the court stated Butamax engaged in lexicography by defining KARI "by its 'use' of NADPH," but then morphed that "definition" to mean "NADPH-dependent." A00020.

however, a patentee must clearly express that intent in the written description."[199] Further, to find disavowal of claim scope, as the district court has, there must be "expressions of manifest exclusion or restriction."[200] Here, there was no such "manifest intent" to exclude NADH-dependent KARIs. According to the specification's express description of KARI, any enzyme that can catalyze AL to DHIV using NADPH is a KARI, regardless of whether it also is "NADH-dependent."[201]

This error—changing the patents' express description to import a negative limitation—mirrors *Martek Biosciences Corp. v. Nutrinova., Inc.*, 579 F.3d 1363 (Fed. Cir. 2009). There, a patent's claims were directed to raising an animal with high concentrations of omega-3 fatty acids. The district court construed the term "animal," finding the patentee acted as a lexicographer. Like the district court here, rather than adopt the specification's express phrasing of "any organism belonging to the kingdom *Animalia*," the court excluded humans from that definition because the specification's embodiments referred only to non-

[199] *Helmsderfer v. Bobrick Washroom Equip., Inc.*, 527 F.3d 1379, 1381 (Fed. Cir. 2008) (emphasis added).

[200] *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1327 (Fed. Cir. 2002); *see Thorner*, 669 F.3d at 1367-68.

[201] *See, e.g.*, *A.B. Dick Co. v. Burroughs Corp.*, 713 F.2d 700, 703 (Fed. Cir. 1993) ("[O]ne cannot avoid infringement merely by adding elements if each element recited in the claims is found in the accused device.").

human animals.[202] This Court reversed, noting "when a patentee explicitly defines a claim term in the patent specification, the patentee's definition controls."[203] "[T]he patentee has used no words or expressions that manifestly exclude coverage of humans, and thus, it would be improper to override the patentee's express definition of 'animal' to limit the scope of the claims."[204]

Here, the error is far clearer than in *Martek*. The specification's "definition" of KARI not only lacks "words or expressions of manifest exclusion'" of non-NADPH-dependent KARIs, but the court's construction reads out embodiments expressly claimed by claim 14 of the '889 patent and claim 15 of the '188 patent.[205] To the extent lexicography applies, "the definition selected by the patent applicant controls,"[206] and KARI must mean "an enzyme that catalyzes the conversion of [AL] to [DHIV] using NADPH … as an electron donor."[207]

2. The Court Erred by Relying Virtually Entirely on Extrinsic Evidence to Redefine KARI

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[202] *Martek*, 579 F.3d at 1380.

[203] *Id*. at 1381 (citations omitted).

[204] *Id*.

[205] *Id*.; *see also Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1120-21 (Fed. Cir. 2004).

[206] *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1249 (Fed. Cir. 1998).

[207] A00152, 7:35-40.

Having it both ways, the district court found Butamax acted as its own lexicographer, but then relied on extrinsic evidence to reinterpret that "definition." Under well settled law, however, where a patentee "explicitly define[s]" a claim term, "extrinsic evidence is simply irrelevant."[208] Ignoring this prohibition, the court's extrinsic evidence analysis practically doubled its review of the misapplied intrinsic evidence, citing references not briefed.[209] Indeed, the court searched for extrinsic support for its erroneous "dependent" construction, which included citing textbooks on metabolic engineering published five-to-seven years *after* the Butamax Patent applications.[210] Extrinsic evidence cannot be used "to alter a claim construction dictated by a proper analysis of the intrinsic evidence,"[211] nor should art long after the filing date be used to analyze the claims, as meanings can change.[212] Because the court placed undue weight on extrinsic evidence to reinterpret the specification's description of KARI, it compels reversal.

C. The District Court's Construction Renders the KARI Term Indefinite

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[208] *Martek*, 579 F.3d at 1382 (citing *Honeywell Int'l, Inc. v. Universal Avionics Sys. Corp.*, 493 F.3d 1358, 1361 (Fed. Cir. 2007)).

[209] A00012-20; A00040.

[210] A00040, n.25 (citing metabolic textbooks not provided by the parties published in 2012 and 2010, and noting "cofactor dependency is extensively analyzed").

[211] *On-Line*, 386 F.3d at 1139.

[212] *Phillips*, 415 F.3d at 1313 ("We have made clear, moreover, that the ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention.…").

Despite KARI having a clear plain meaning, and description in the specification, the court construed KARI in a manner which it acknowledged lacked clear metes and bounds, or measure.[213] The construction should have been rejected on that basis. Inexplicably, however, the court adopted it, "couldn't discern what the right measurement was",[214] and then "le[ft] the explanation of this term of art at trial to the parties' scientific experts."[215] Because the interpretation makes a definite term indefinite, it should be reversed.

A term is indefinite if its legal scope is not clear enough that a POSA could determine whether a particular composition infringes or not.[216] In contrast, a claim is definite where a POSA "would understand the bounds of the claim when read in light of the specification."[217]

Here, the specification provides a clear description and test for KARI "measured using" the Arfin assay.[218] Because a POSA would "readily discern the boundary" of what is a KARI according to that description, it should have been

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[213] A00040, n.25; A10830, 8:8-9.

[214] A10830, 8:8-9.

[215] A00040, n.25.

[216] *See* 35 U.S.C. § 112 (2000); *Geneva Pharm. Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1384 (Fed. Cir. 2003).

[217] *Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001).

[218] A00165, 34:17-19.

adopted.[219] Instead, the court construed KARI as NADPH-dependent and, at a loss to define what this means, washed its hands of the matter, leaving the parties' experts to debate it at trial. Yet, a jury "cannot be left free to apply its own reading of disputed terms to the facts of the case."[220] The court's decision would have created a trial over the expert's subjective understanding of the claims' meaning rather than whether Gevo's product fell within them—an erroneous result, contrary to the purpose *Markman*.[221]

The court's extraordinary measures to keep this construction—reviewing literature not briefed, and divesting itself of deciding the construction's meaning after that review failed to define the term— shows that its construction is indefinite and incorrect. As Gevo's own expert testified, the dividing line between "dependent" enzymes has a "gray area" and "it really would depend on who you're talking to."[222] Similarly, Butamax's expert testified the patents do "not lay out

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[219] *Wellman*, 642 F.3d at 1367 (reversing indefinite construction, noting the specification disclosed a test allowing one to "readily discern the boundary" of what was claimed).

[220] *Sulzer Textil A.G. v. Picanol N.V.*, 358 F.3d 1356, 1366 (Fed. Cir. 2004).

[221] *See, e.g.*, *O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co., Ltd.*, 521 F.3d 1351, 1360-63 (Fed. Cir. 2008) ("When the parties present a fundamental dispute regarding the scope of a claim term, it is the court's duty to resolve it."); *CytoLogix*, 424 F.3d at 1173 (stating it is "improper" to allow "conflicting claim constructions to [be argued] to the jury").

[222] A00038-A00039 & n.22; A09633, 380:18-381:25.

definitions for things that are NADH depend[ent], NADPH dependent, dual dependent, and absent such definitions, they really can't be applied."[223]

Moreover, the term NADPH-dependent is indefinite here because the same enzyme may or may not be dependent on a given cofactor depending on how it is examined. When tested in the Arfin assay, with only NADPH present, a KARI will only use that cofactor.[224] When tested in an assay with only NADH, that same enzyme will only use that cofactor.[225] In a competitive binding experiment, imagined by Gevo's expert, "gray areas" arise.[226] Thus, the same KARI could be "dependent" or not depending on the test used, making the construction "the epitome of indefiniteness," and requiring its reversal.[227]

V. Gevo Infringes the Claims as Properly Construed[228]

Whether according to KARI's plain meaning, or the "definition" in the specification, Gevo's products literally infringe the Butamax Patents.

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[223] A09780, 131:10-132:4.

[224] A00011, n.4.

[225] *Id*.

[226] A00038-39, n22.

[227] *Geneva*, 349 F.3d at 1384.

[228] At summary judgment, Gevo raised one non-infringement argument unrelated to the KARI element based solely on attorney argument lacking any expert or factual support. A10143-A10144. Thus, should the Court reverse the KARI construction, Gevo literally infringes the asserted claims.

[redacted] and in public and [redacted] Gevo expressly described its isobutanol pathway as including a KARI enzyme having EC 1.1.1.86.[230] After being sued, Gevo made up a new name for its KARIs, called "NKR," based on the advice of counsel.[231] However, when under oath, even Gevo's non-infringement expert admitted Gevo's enzymes "meet the definition of an [aceto] hydroxy acid isomeroreductase enzyme."[232] These enzymes are 98% identical to the preferred KARI sequences in the Butamax Patents, and 99% identical to other KARIs having EC 1.1.1.86.[233]

Critically, Gevo's KARIs also catalyze AL to DHIV using NADPH as an electron donor measured using the Arfin assay. Their specific activity with NADPH exceeds the level reported by the Butamax Patents by *four-to-six times*.[234] Their activity equals other published KARI enzymes cited in BRENDA[235]—the

[229] *Supra* n.107. Several of Gevo's experts agreed that the term "NKR" has never been used outside the context of this litigation or by anyone other than Gevo. A09709-A09710, 61:25-62:6; A09715, 178:4-10.

[230] *Supra* n.103, n.104, n.105.

[231] *Supra* n.106.

[232] *Supra* n.108.

[233] *Supra* n.111, n.112.

[234] *Supra* n.102.

[235] *Supra* n.114.

database the inventors cited during patent prosecution[236]— and is similar to and higher than other wild-type KARIs.[237] Their activity is also [redacted] Finally, Butamax's testing expert confirmed Gevo's KARIs have statistically significant activity with NADPH in the Arfin assay.[239]

Gevo's response is that its KARIs have only "ancillary" activity with NADPH.[240] This assertion is legally irrelevant and factually erroneous. On the law, this Court has refused to excuse literal infringement on the grounds of it being "*de minimis*."[241] Nor does it matter if Gevo's KARIs use NADPH in a less than optimal way or only sometimes.[242] On the facts, Gevo's KARIs have *substantial* activity in the Arfin assay. Putting context to these numbers is helpful. One of Gevo's KARIs has a specific activity with NADPH of 0.15 units/mg.[243] This

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[236] *Supra* n.115.

[237] A09895.

[238] *Supra* n.116.

[239] *Supra* n.117.

[240] A00039.

[241] *See, e.g.*, *Embrex, Inc. v. Service Eng'g Corp.*, 216 F. 3d 1343, 1353 (Fed. Cir. 2000) (Rader, J., concurring).

[242] *Bell Commc'ns Research, Inc. v. Vitalink Commc'ns Corp.*, 55 F.3d 615, 622-623 (Fed. Cir. 1995); *Paper Converting Mach. Co. v. Magna-Graphics Corp.*, 745 F.2d 11, 20 (Fed. Cir. 1984).

[243] *Supra* n.102. The other KARI has a specific activity of 0.1 units/mg, meaning 60,000 trillion NADPH molecules are used per minute.

means that for every milligram of that enzyme—about a grain of sand—90,000 trillion molecules of NADPH are used per minute while converting AL to DHIV.[244] If NADPH were dollars, a speck of this KARI would use the entire national debt in one hundredth of one second. Without a KARI, the odds of this reaction occurring even once per minute are infinitesimal. Such activity can hardly be considered ancillary, and, is several times greater than the example of KARI activity in the Butamax Patents.[245]

Gevo also responds that its KARIs do not infringe because they use NADH;[246] however, this too is irrelevant: "[O]ne cannot avoid infringement merely by adding elements if each element recited in the claims is found in the accused device."[247] "Nor is infringement avoided if a claimed feature performs not only as shown in the patent, but also performs an additional function."[248] Rather, Gevo's KARIs' activity with NADH proves infringement not only of the independent claims, but also of claim 14 of the '889 patent, which recites "one or more enzymes [of claim 1] uses NADH as an electron donor."[249]

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[244] *Supra* n.69.

[245] *Supra* n.102.

[246] A00039.

[247] *See A.B. Dick*, 713 F.2d at 703.

[248] *N. Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 945 (Fed. Cir. 1990).

[249] A00487.

VI. The District Court Erred in Granting Summary Judgment of No DOE Infringement

Even under the district court's claim construction, Gevo's products infringe under the DOE. On summary judgment Gevo moved for no DOE infringement based only on prosecution history estoppel.[250] Butamax replied that estoppel did not apply,[251] and that there are numerous issues of disputed fact concerning DOE infringement even under Gevo's construction. Again going beyond the parties' briefing, the court granted summary judgment of no DOE infringement on a basis not asserted by Gevo—that NADH and NADPH are not insubstantially different. The court also failed to address Butamax's substantial evidence of DOE infringement.

A. The Court Committed Legal Error, Focusing the DOE Analysis on Unclaimed Subject Matter

"The proper inquiry" for DOE is "whether an asserted equivalent represents an 'insubstantial difference' from the claimed element" in dispute, or "whether the substitute element matches the function, way, and result of the

[250] A10098.

[251] It does not apply because the limitation allegedly met by equivalents—"NADPH-dependency"—was not made during the prosecution by amendment, but read in by the district court. *Festo Corp. v. Shoketsu Kinzoku Koguyo Kabushiki, Inc*. 535 U.S. 722, 737 (2002) (noting the reach of estoppel is based on the subject matter surrendered by the narrowing amendment). During prosecution, the inventors made clear they covered KARI as an entire class. *Supra* sects. I.A.4, IV.A.5; A07583; A07143; A04780; A04792.

claimed invention."[252] "An analysis of the role played by each element *in the context of the specific patent claim* is required."[253]

Here, the court granted summary judgment based on presumed facts that NADH and NADPH are not insubstantially different in natural metabolism.[254] But, these cofactors are not elements of the independent claims. By going beyond the briefing, the court legally erred[255] because the claims are to recombinant microorganisms and processes that express an engineered pathway, which produce isobutanol. They are *not* to cofactors. As KARI is the one element Gevo contends it does not literally meet, DOE turns on whether Gevo's KARIs are equivalent to "an enzyme known by EC number 1.1.1.86 that catalyzes the conversion of acetolactate to 2,3-dihydroxyisovalerate and is NADPH-dependent," as the court construed the term.[256]

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[252] *Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1356 (Fed. Cir. 2012); *see also Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 608 (1950).

[253] *Warner-Jenkinson Co., Inc. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 40 (1997) (emphasis added).

[254] A00041.

[255] *Weiss v. Reebok Int'l Ltd., Inc.*, 91 Fed. App'x 683, 689 (Fed. Cir. 2004) ("A court should be cautious in this situation in which summary judgment is granted on unbriefed grounds inasmuch as there is a greater possibility of error.") (citations omitted)).

[256] *Brilliant Instruments, Inc. v. GuideTech, LLC*, 707 F.3d 1342, 1347-49 (Fed. Cir. 2013) (reversing summary judgment of non-infringement for failure to engage in proper DOE inquiry); *Deere*, 703 F.3d at 1356-57.

On this issue, the district court itself ruled there was a genuine issue of material fact regarding literal infringement.[257] Thus, there also must be an issue of fact with respect to DOE.[258] By focusing on a purported "not insubstantial difference" between NADH and NADPH—the cofactors rather than the enzymes—the court "shortcut" the DOE inquiry and identified a false "'binary' choice in which an element is either present or 'not present.'"[259] However, the court itself noted the dividing line of a KARI that is NADH or NADPH-dependent was a "gray area."[260] And, the DOE analysis is "not susceptible to the black and white categorization made by the district court."[261]

B. Substantial Evidence of Equivalence Between Gevo's KARI and the Claimed KARI Precludes Summary Judgment of No DOE

"Infringement under the doctrine of equivalents requires an intensely factual inquiry,"[262] and summary judgment of no DOE infringement will only be affirmed "if the record contains no genuine issue of material fact and leaves no

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[257] A00040.

[258] *See, e.g.*, *IMS Tech., Inc. v. Haas Automation, Inc.*, 206 F.3d 1422, 1437 (Fed. Cir. 2000) (noting an issue of fact existed for literal infringement, thus, an issue of fact remained for DOE).

[259] *Deere,* 703 F.3d at 1356.

[260] A00038-A00039, n.22 (citing Gevo's expert's testimony).

[261] *Goldenberg v. Cytogen, Inc.*, 373 F.3d 1158, 1168 (Fed. Cir. 2004) (reversing summary judgment of no DOE where the trial court's analysis created a false dichotomy).

[262] *Leggett & Platt, Inc. v. Hickory Springs Mfg.*, 285 F.3d 1353, 1357 (Fed. Cir. 2002) (quotations omittted).

room for a reasonable jury to find equivalence."[263] Thus, "ordinarily" DOE is a "reserved for the fact finder."[264]

Butamax provided substantial evidence that Gevo's KARIs are equivalent to "an enzyme known by EC number 1.1.1.86 that catalyzes the conversion of acetolactate to 2,3-dihydroxyisovalerate and is NADPH-dependent." The evidence of literal infringement set out above alone should be sufficient to warrant trial on DOE infringement.

Even if Gevo's KARIs used only NADH, they would be insubstantially different from a "NADPH-dependent KARI," and perform the same function-way-result in the claimed engineered pathway, by converting AL to DHIV. Gevo's expert admitted both enzymes function with substrate AL in the same manner: "NADPH donates a hydride to the acetolactate intermediate from wild-type enzyme [KARI]. NADH donates the hydride to the same substrate from [Gevo's] enzymes."[265] He also admitted an NADPH-dependent enzyme transfers the electrons in the same way as Gevo's KARI: "The mechanism of hydride

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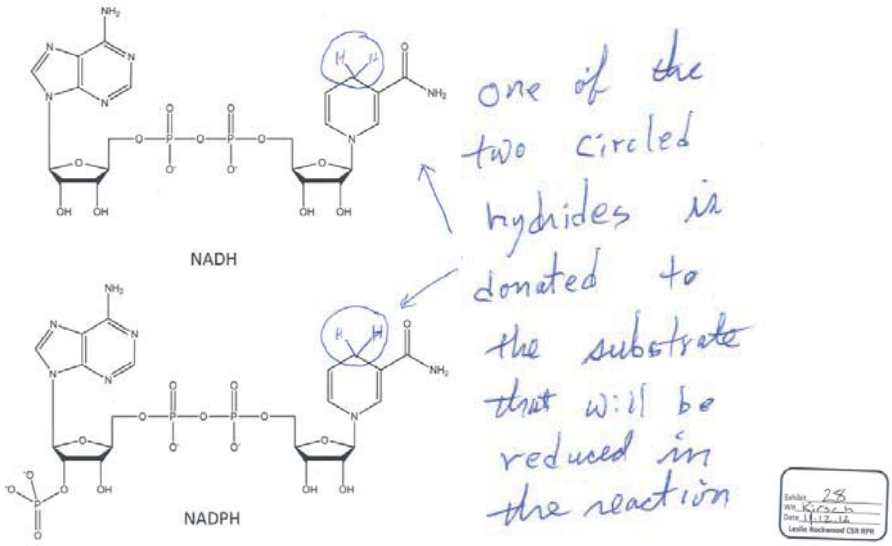
[263] *Id.*

[264] *Deere*, 703 F.3d at 1356 (citing *Warner-Jenkinson*, 520 U.S. at 38-39).

[265] A09631, 369:23-370-22.

transfers is the same for the two, yes."[266] And he admitted the enzymes produce the same result, stating the product "DHIV is the same, yes."[267]

In hand-drawn notations, Gevo's expert also indicated that Gevo's KARIs use two electrons in the form of a hydride (H^-) from NADH at the identical position that a NADPH-dependent KARI uses them from NADPH[268]:



Butamax's infringement expert also provided particularized testimony on why Gevo's KARIs are equivalent to the claimed KARI[269]:

> A. It's an insubstantial difference with respect to the function of the enzyme the way it occurs and the product that results.
>
> Q. Okay. So what is your understanding of the function of NADH with respect to Gevo's KARI?

[266] A09632, 379:19.

[267] A09631, 371:15.

[268] A10598.

[269] A10564, 279:25-280:25.

> A. It's involved in moving electrons between the -- from the substrate to the product.
>
> Q. Does that function in the same way as NADPH?
>
> A. In essentially the same way.
>
> Q. Do they both donate a hydride?
>
> *********
>
> THE WITNESS: Yes.
>
> Q. Okay. And is there anything different with their reducing potential between these two cofactors?
>
> A. I don't believe so. It's close.
>
> Q. ...Gevo's KARIs, do they also produce a product called DHIV?
>
> *******
>
> THE WITNESS: Yes.
>
> Q. And do they do that regard --with either NADPH or NADH?
>
> A. Yes.

This evidence was unrebutted. And although the district court was required to draw "all reasonable inferences in favor" of Butamax[270], the court failed to even address Butamax's evidence, and focused on the purported differences between NADH and NADPH in natural metabolism, *not* in an

[270] *Leggett*, 285 F.3d at 1359-60 (reversing summary judgment of no DOE infringement, where district court made "summar[]y conclu[sions]" and failed to draw all reasonable inferences in favor of the non-movant).

engineered pathway.[271] Even assuming that were relevant to DOE, Butamax also provided substantial evidence that the cofactors' are insubstantially different, which the court also disregarded. Butamax's expert noted "[a] well regarded textbook in the field describes the differences between" NADPH and NADH "as 'trivial' in chemical terms."[272] The diagram above signed by Gevo's expert, further shows these cofactors react identically during conversion of AL to DHIV.[273] Thus, with respect to the disputed KARI element and AL to DHIV conversion, NADH and NADPH serve the same purpose to donate electrons. They do that in substantially the same way and yield the same result. By disregarding Butamax's evidence and deciding contested issues of fact, the court "invaded the province of the finder of fact" and summary judgment should be reversed.[274]

VII. The District Court Erred in Holding Claim 12 and 13 of the '889 Patent to Be Invalid for Lack of Written Description

Compliance with the written description requirement is a question of fact regarding whether the patent's description "clearly allow[s] persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed"

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[271] *Id*.

[272] A04594, ¶35; A05375; A04586-A04587 ¶20.

[273] *See also compare* A09849, *with* A09851 (Gevo's expert illustrating that the identical AL to DHIV conversion occurs with the different cofactors).

[274] *Dorel Juvenile Grp. Inc. v. Graco Children's Prods. Inc.*, 429 F.3d 1043, 1047 (Fed. Cir. 2005).

or "that the inventor had possession of the claimed subject matter as of the filing date."[275]

Claim 12 recites "the recombinant yeast microorganism of claim 1 wherein the said microorganism further comprises inactivated genes thereby reducing yield loss from competing pathways for carbon flow." Claim 13 depends on claim 12 and recites "wherein said inactivated genes reduce pyruvate decarboxylase activity."

The specification states "[t]here is a need… for an environmentally responsible, cost-effective process for the production of isobutanol as a single product,"[276] and to achieve that, "[t]he microbial host also has to be manipulated in order to inactivate competing pathways for carbon flow by deleting various genes."[277] The specification also identifies pyruvate decarboxylase (PDC) as an enzyme that causes misdirection of carbon away from isobutanol production stating: "*To prevent misdirection of pyruvate away from isobutanol production,* a decarboxylase with decreased affinity for pyruvate is desired."[278]

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[275] *See Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*) (citations and quotation marks omitted).

[276] A00324, 1:63-1:65.

[277] A00331, 16:55-57.

[278] A00329, 12:12-12:17 (emphasis added).

Based on this disclosure, the court agreed that the '889 patent may be interpreted as identifying "the problem and the solution" of carbon loss causing reduced yield of isobutanol.[279] However, the court ruled claims 12 and 13 invalid because it found no genuine dispute of fact that the specification does not "describe how to put into practice the solution."[280]

To the contrary, Butamax's expert explained these disclosures teach "both the problem—competing pathways, such as 'the misdirection of pyruvate away from isobutanol production'—*and the solution*—'inactivat[ion of] competing pathways for carbon flow by deleting various genes."[281] Indeed, there is verbatim support in the specification for claim 12, and the negative limitation of PDC deletion for claim 13 is supported by the specification's express instruction to avoid misdirection of pyruvate.[282] Gevo's invalidity expert admitted that deletion of competing pathways was conventional by 2005, and deletion of PDC was specifically described by the '889 patent[283]:

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[279] A00053.

[280] *Id*.

[281] A03147, ¶61 (emphasis added); A03143-A03144, ¶54; A10427-A10428, ¶¶219-20.

[282] *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1351 (Fed. Cir. 2012) (finding adequate description in specification that "describes a reason to exclude the relevant limitation").

[283] A10448, 260:2-25.

> Q. Okay. So you agree that the concept of deleting competing pathways was conventional by 2005?
>
> *********
>
> A. It's -- if anything, it's in my book, showing that the concept that you want to eliminate side reactions, what we call side…
>
> **********
>
> Q. Okay. *So when the patent says you want to get rid of competing pathways, what does that tell you*?
>
> A. Nothing new.
>
> Q. *Well, does it tell you want to delete PDC***?**
>
> **********
>
> A. *Yes*.

He further testified the specification's discussion of the "need, therefore, for an environmentally responsible, cost effective process for the production of isobutanol as a single product," "completely" informs a POSA to delete PDC in yeast[284]:

> Q. *Okay. So then this sentence of single product tells you you're knocking out PDC*?
>
> ********
>
> A. *Completely.*
>
> Q. Thank you.
>
> A. It tells you that you're knocking out PDC completely, then you're not making any ethanol.

[284] A10449, 262:20-263:24.

Another Gevo expert also admitted that based on the specification, he would understand that "you want to knock out PDC," and that "you do want to knock out the … the pyruvate decarboxylase that leads to acetaldehyde."[285]

These admissions of adequate description of inactivating genes (claim 12) and inactivation of PDC (claim 13) alone are sufficient to deny Gevo's summary judgment motion.[286] In combination with the affirmative evidence from Butamax's expert, there is far more than sufficient evidence to withstand summary judgment.

The district court further erred by dismissing the '889 patent's citation to the Dickinson reference,[287] which expressly discloses PDC deleted yeast.[288] The court discounted it, stating it "does not supplement the specification in such a way as to provide a sufficient written description."[289] However, that reference (and numerous others cited by Butamax's expert[290]) shows that engineering of PDC-minus yeast was well-known in the art prior to 2005, and known to the inventors. Indeed, PDC-minus yeast was *commercially available* with the American Type

[285] A10492, 271-72.

[286] *See*, *e.g.*, *Space Sys./Loral, Inc. v. Lockheed Martin Corp.*, 405 F.3d 985, 988-90 (Fed. Cir. 2005).

[287] A00054.

[288] A10427, ¶219.

[289] A00054.

[290] A03141-A03142, ¶48 (citing, *e.g.*, van Maris (2004), Filkweert (1999), Hohmann (1993), and Hollenberg (1990)).

Culture Collection by 1993.[291] As such, putting the claimed engineered pathway into such commercial yeast would be readily achieved by a POSA.[292] These are factors that must be taken into account in the written description analysis, but were not.[293] Thus, based on the specification's teaching—which both parties' experts agree describes inactivating genes, including PDC—in view of the well-known available art, a POSA would have understood claims 12 and 13 are adequately described.[294] At a minimum, there is sufficient evidence from which a reasonable jury could find on behalf of Butamax on this issue.

VIII. The Order's Statement of Invalidity of Claims 12 and 13 Based on Enablement Must Be Reversed

The court's order, invalidating claim 12 and 13 of the '889 patent based on lack of enablement, can only be regarded as a scrivener's error that must be reversed.[295] Gevo did not move on this basis, and the court's opinion lacks *any* discussion of this issue for claims 12 and 13. Basic due process would have required the court to provide Butamax notice and a fair opportunity to present

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[291] A10428, ¶221.

[292] A10448, 260:2-25; A03141-A03143; A03141-A03143, ¶¶48-52; A03147, ¶63.

[293] *See Ariad*, 598 F.3d at 1351 (factors include "the existing knowledge in the particular field" and "the extent and content of the prior art").

[294] *Cf. Streck, Inc. v. Research & Diagnostic Sys., Inc.*, 665 F.3d 1269, 1287 (Fed. Cir. 2012).

[295] A00059.

evidence in opposition if the court had intended to rule on this issue.[296] The court did not, and the order erroneously conflated the separate written description and enablement requirements. Moreover, despite not being afforded an opportunity to address this issue, at a minimum, the record contains substantial evidence that these claims are not invalid for lack of enablement.[297] Therefore, this portion of the order must be reversed.

CONCLUSION

This Court should reverse the construction of "acetohydroxy acid isomeroreductase" and direct the entry of judgment of Gevo's literal infringement of the asserted claims of the Butamax Patents. This Court should also vacate the district court's order of no infringement under DOE and invalidity of claims 12 and 13 of the '889 patent and remand for further proceedings.

[296] *See, e.g., Bemis Mfg. v. Dornoch Med. Sys., Inc.*, 21 Fed. App'x 930, 935 (Fed. Cir. 2001).

[297] Butamax's expert opined that claims 12 and 13 are enabled. *See, e.g.*, A03141-A03143, ¶¶48-52.

May 31, 2013

Respectfully submitted,

/s/ Peter B. Silverman

Leora Ben-Ami
Thomas F. Fleming
Christopher T. Jagoe
Peter B. Silverman
KIRKLAND & ELLIS LLP
601 Lexington Avenue
New York NY 10022
(212) 446-4800

Counsel for Plaintiff -Appellant
Butamax™ Advanced Biofuels LLC

CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION

I certify that this brief complies with the type-volume limitation specified in Federal Rule of Appellate Procedure 32(a)(7)(B). According to the word processing system used to prepare this brief, Microsoft Word 2007, the brief contains 13,897 words.

May 31, 2013 */s/ Peter B. Silverman*

PROOF OF SERVICE

I hereby certify that I caused the foregoing Non-Confidential Opening Brief for Plaintiff-Appellant Butamax™ Advanced Biofuels LLC to be served on All Counsel via Electronic Mail generated by the Court's electronic filing system (CM/ECF) with a Notice of Docket Activity to the below-listed counsel and via two (2) copies via Federal Express Next Business Day Delivery to:

Michelle Rhyu (rhyums@cooley.com)
Stephen C. Neal (nealsc@cooley.com)
Benjamin G. Damstedt
(bdamstedt@cooley.com)
Daniel J. Knauss (dknauss@cooley.com
COOLEY LLP
Five Palo Alto Square,
3000 El Camino Real
Palo Alto, CA 94306-2155
Tel: (650) 843-5000

James P. Brogan
(jbrogan@cooley.com)
COOLEY LLP
380 Interlocken Crescent, Suite 900
Broomfield, CO 80021
Tel: (720) 566-4000

I also certify that I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Federal Circuit by using the appellate CM/ECF system on this 31st day of May, 2013.

Six hard copies of the foregoing Non-Confidential Opening Brief for Plaintiff-Appellant Butamax™ Advanced Biofuels LLC will be sent to the Clerk's Office by Federal Express Next Business Day delivery upon the Court's approval to:

Clerk of Court
United States Court of Appeals, Federal Circuit
717 Madison Place, NW, Room 401
Washington, DC 20439
Telephone: (202) 633-6550

/s/ Ramiro A. Honeywell
Sworn to me this

May 31, 2013

RAMIRO A. HONEYWELL
Notary Public, State of New York
No. 01HO6118731
Qualified in Kings County

/s/ Nadia Oswald-Hamid
Nadia Oswald-Hamid

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

BUTAMAX™ ADVANCED BIOFUELS LLC,	)	
Plaintiff/Counterclaim Defendant	)	
v.	)	Civ. No. 11-54-SLR
GEVO, INC.,	)	
Defendant/Counterclaim Plaintiff	)	
v.	)	
E.I. DUPONT DE NEMOURS AND COMPANY,	)	
Counterclaim Defendant	)	

Richard L. Horwitz, Esquire and David E. Moore, Esquire of Potter, Anderson & Corroon LLP, Wilmington, Delaware. Counsel for Plaintiff. Of Counsel: Leora Ben-Ami, Esquire, Thomas F. Fleming, Esquire, Christopher T. Jagoe, Esquire and Patricia A. Carson, Esquire, Daniel Forchheimer, Esquire, and Peter B. Silverman, Esquire of Kirkland & Ellis LLP.

Thomas C. Grimm, Esquire and Jeremy A. Tigan, Esquire of Morris, Nichols, Arsht & Tunnell LLP, Wilmington, Delaware. Counsel for Defendant. Of Counsel: Stephen C. Neal, Esquire, Michelle S. Rhyu, Esquire, Benjamin G. Damstedt, Esquire, Daniel J. Knauss, Esquire of Cooley LLP.

MEMORANDUM OPINION

Dated: March 19, 2013
Wilmington, Delaware

ROBINSON, District Judge

I. INTRODUCTION

On January 14, 2011, plaintiff Butamax™ Advanced Biofuels LLC ("Butamax") filed suit in this district against defendant Gevo, Inc. ("Gevo") alleging infringement of U.S. Patent No. 7,851,188 ("the '188 patent"). (D.I. 1) The '188 patent discloses and claims "a recombinant microorganism having an engineered isobutanol biosynthetic pathway" that "may be used for the commercial production of isobutanol." ('188 patent, 2:3-6) Gevo answered the complaint on March 25, 2011. (D.I. 10) On August 11, 2011, Butamax filed an amended complaint, alleging that Gevo also infringed U.S. Patent No. 7,993,889 ("the '889 patent"). (D.I. 41) The '889 patent was filed as a divisional application from the '188 patent and claims a method for isobutanol production using recombinant microorganisms with an engineered biosynthetic pathway. ('889 patent, 2:3-6)

Gevo answered the amended complaint on September 13, 2011 and counterclaimed against Butamax and E.I. DuPont De Nemours and Company ("DuPont") alleging infringement of U.S. Patent Nos. 8,017,375 ("the '375 patent") and 8,017,376 ("the '376 patent"), also related to the production of isobutanol from recombinant microorganisms. (D.I. 52) Butamax and DuPont answered the counterclaims on November 18, 2011 and counter-counterclaimed against Gevo seeking a declaratory judgment on non-infringement and invalidity of the '375 patent and the '376 patent. (D.I. 117) On December 9, 2011, Gevo answered the counter-counterclaims. (D.I. 130) On February 24, 2012, Butamax and DuPont filed a motion to sever Gevo's counterclaims, which was granted. (D.I. 213, D.I. 371) On June 21,

2012, upon the grant of its timely motion to amend, Butamax and DuPont amended its answer to the counterclaims and the counter-counterclaims adding affirmative defenses and counter-counterclaims of inequitable conduct. (D.I. 372) Gevo's untimely motion, filed June 29, 2012, seeking to amend its answer and counterclaims to include an affirmative defense and counterclaim of inequitable conduct was denied. (D.I. 388; D.I. 693)

On September 22, 2011, Butamax filed a motion for preliminary injunction which sought to enjoin Gevo from infringing the '889 patent. (D.I. 61) After an evidentiary hearing on the matter, March 1-2, 2012, the court denied Butamax's motion for preliminary injunction on June 19, 2012. (D.I. 370) On June 25, 2012, Butamax appealed this decision. (D.I. 376) On December 26, 2012, the Federal Circuit affirmed this court's denial of the preliminary injunction. *Butamax Advanced Biofuels LLC v. Gevo, Inc.*, No. 12-1490 (Fed. Cir. Nov 16, 2012).

Presently before the court are several motions for summary judgment: Butamax's summary judgment motion of infringement of the '188 and '889 patents (D.I. 595) and cross-motion of no invalidity of the '889 patent (D.I. 622), as well as Gevo's motions for summary judgment of invalidity and non-infringement of the '188 and '889 patents. (D.I. 598; D.I. 610) Butamax and DuPont also filed a motion to exclude testimony by Gevo's experts with respect to the '188 patent and '376 patent. (D.I. 640) The court herein addresses this motion as it relates to the '188 patent and reserves its decision as it relates to the '376 patent. The court has jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a).

II. BACKGROUND

A. The Parties

Butamax is a limited liability corporation organized and existing under the laws of the State of Delaware, with its principal place of business in Wilmington, Delaware. (D.I. 41 at ¶ 1) Butamax develops methods of making biofuels such as biobutanol, a product which may be used as a fuel or as a feed-stock chemical in the production of various plastics, fibers and other products. (*Id.*) In particular, Butamax has developed a biological method of producing isobutanol, a type of biobutanol. (*Id.*)

Gevo is a corporation organized and existing under the laws of the State of Delaware, with its principal place of business in Englewood, Colorado. (D.I. 52 at 5 ¶ 1) Gevo is also involved in the commercial-scale production of isobutanol using biological methods. (*Id.* at ¶ 11; D.I. 154 at 3)

DuPont is a corporation organized and existing under the laws of the State of Delaware, with its principle place of business in Wilmington, Delaware. (D.I. 470 at 9 ¶ 2) DuPont is engaged in research and development relating to the production of isobutanol. (*Id.* at 1 ¶ 5)

B. Technology

Isobutanol is an industrial chemical that may be blended with gasoline-based fuels as an alternative to ethanol, the current dominant biofuel in gasoline blends. ('889 patent, 6:38-40) Isobutanol is preferred over ethanol because it has a higher energy content and is less corrosive. ('889 patent, 6:33-40) Butamax proposes a method of producing isobutanol using genetically-engineered yeast microorganisms that promises to facilitate the transition to renewable transportation fuels and reduce greenhouse gas

emissions. (D.I. 41 at ¶ 1)

This improved method for producing isobutanol is achieved by introducing engineered deoxyribonucleic acid ("DNA") into microorganisms in order to stimulate isobutanol production. (*Id.* at ¶ 12; '889 patent, 17:9-19) Microorganisms such as yeast and bacteria are capable of producing isobutanol through a five-step pathway consisting of the following five chemical conversions: (1) pyruvate to acetolactate; (2) acetolactate to 2,3-dihydroxyisovalerate; (3) 2,3-dihydroxyisovalerate to α-ketoisovalerate; (4) α-ketoisovalerate to isobutyraldehyde; and (5) isobutyraldehyde to isobutanol. (D.I. 41 at ¶ 12; '889 patent, 325:19-30) The engineered DNA constructs encode enzymes that catalyze, or increase the chemical reaction rate, of the five steps in the isobutanol biosynthesis pathway. (D.I. 41 at ¶ 12; '889 patent, 325:32-42) Introducing these enzyme-coding DNA constructs into the microorganism stimulates the biosynthetic pathway and increases overall isobutanol production. (D.I. 41 at ¶ 12; '889 patent, 44:28-32)

C. The Patents

The '188 patent, entitled "Fermentive Production of Four Carbon Alcohols," was filed on October 25, 2006 and issued on December 14, 2010. It claims priority from provisional application No. 60/730,290 which was filed on October 26, 2005. The '889 patent was filed on January 23, 2008 and issued on August 9, 2011. The '889 patent is a divisional application of the '188 patent. Both the '889 patent and the '188 patent are assigned to Butamax. (D.I. 41 at ¶¶ 6, 9)

The specifications of the '188 and '889 patents admit that isobutanol may be chemically synthesized from starting materials derived from petrochemicals, but this

method of synthesis is expensive and bad for the environment. ('889 patent, 1:33-35; '188 patent, 1:33-35) The inventors assert that using yeast or other comparable microorganisms to produce isobutanol would reduce greenhouse gas emissions and, therefore, would be a desirable alternative to chemical synthesis. ('889 patent, 1:36-38; '188 patent, 1:36-38)

Yeast naturally produce low levels of isobutanol as a by-product of fermentation. ('889 patent, 1:39-49; '188 patent, 1:39-49) More specifically, isobutanol is produced from the catabolism, or metabolic breakdown, of the amino acid L-valine. ('889 patent, 1:39-49; '188 patent, 1:39-49) However, use of L-valine on an industrial scale as a feed-stock for yeast fermentation is prohibitively expensive. ('889 patent, 1:57-59; '188 patent, 1:57-59) The inventors claim a more cost-efficient method of producing isobutanol directly from pyruvate, a product of sugar digestion, in lieu of L-valine. ('889 patent, 325:15-23; '188 patent, 335:20-23) The transformation of pyruvate to isobutanol is achieved through one of four multi-step biosynthetic pathways. ('889 patent, 11:40-43; '188 patent, 12:1-4)

In the claimed biosynthetic pathway, all of the necessary reaction substrates are components of "well-characterized pathways" that are naturally present in yeast. ('889 patent, 11:57-61; '188 patent, 12:19-21) The inventors assert that stimulating this pathway through the introduction of DNA constructs coding for one or more enzymes specific to pathway steps yields increased isobutanol production. ('889 patent, 17:9-19, 44:28-32; '188 patent, 19:45-55, 49:46-51) Although the enzymes are introduced via genetic manipulation, the enzymes also exist in yeast or other microorganisms as naturally-occurring components of the "well-characterized" enzymatic pathways. ('889

patent, 11:58-12:32; '188 patent, 12:19-60)

Independent claim 1 of the '889 patent, reproduced below, describes the preferred biosynthetic pathway and identifies which enzymes catalyze each step of the claimed pathway:

> 1. A method for producing isobutanol comprising;
> a. providing a fermentation media comprising carbon substrate; and
> b. contacting said media with a recombinant yeast microorganism expressing an engineered isobutanol biosynthetic pathway wherein said pathway comprises the following substrate to product conversions;
> i. pyruvate to acetolactate (pathway step a);
> ii. acetolactate to 2,3-dihydroxyisovalerate (pathway step b);
> iii. 2,3-dihydroxyisovalerate to α-ketoisovalerate (pathway step c);
> iv. α-ketoisovalerate to isobutyraldehyde (pathway step d); and
> v. isobutyraldehyde to isobutanol (pathway step e);
> and wherein
> a) the substrate to product conversion of step (i) is performed by an acetolactate synthase enzyme;
> b) the substrate to product conversion of step (ii) is performed by an acetohydroxy acid isomeroreductase enzyme;
> c) the substrate to product conversion of step (iii) is performed by an acetohydroxy acid dehydralase enzyme;
> d) the substrate to product conversion of step (iv) is performed by a decarboxylase enzyme; and
> e) the substrate to product conversion of step (v) is performed by an alcohol dehydrogenase enzyme;
> whereby isobutanol is produced.

('889 patent, 325:15-44) Independent claim 1 of the '188 patent, reproduced below, is directed at the recombinant microbial host cell:

> 1. A recombinant microbial host cell comprising heterologous DNA molecules encoding polypeptides that catalyze substrate to product conversions for each step below:

i) pyruvate to acetolactate;
ii) acetolactate to 2,3-dihydroxyisovalerate;
iii. 2,3-dihydroxyisovalerate to α-ketoisovalerate;
iv. α-ketoisovalerate to isobutyraldehyde;
wherein said microbial host cell produces isobutanol; and wherein
a) the polypeptide that catalyzes a substrate to product conversion of pyruvate to acetolactate is acetolactate synthase having the EC number 2.2.1.6;
b) the polypeptide that catalyzes a substrate to product conversion of acetolactate to 2,3-dihydroxyisovalerate is acetohydroxy acid isomeroreductase having the EC number 1.1.1.86;
c) the polypeptide that catalyzes a substrate to product conversion of 2,3-dihydroxyisovalerate to α-ketoisovalerate is acetohydroxy acid dehydralase having the EC number 4.2.1.9;
d) the polypeptide that catalyzes a substrate to product conversion of α-ketoisovalerate to isobutyraldehyde is branched-chain α-keto acid decarboxylase having the EC number 4.1.1.72.

('188 patent, 335:19-44) Butamax alleges that Gevo's lead strains infringe certain claims of the '188 patent. (D.I. 41 ¶¶ 17-20) Butamax further alleges that Gevo's processes infringe certain claims of the '889 patent. (D.I. 41 ¶¶ 21-23)

III. CLAIM CONSTRUCTION

A. Legal Principles

Claim construction is a matter of law. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1330 (Fed. Cir. 2005) (en banc). Claim construction focuses on intrinsic evidence - the claims, specification and prosecution history - because intrinsic evidence is "the most significant source of the legally operative meaning of disputed claim language." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996); *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S.

370 (1996). Claims must be interpreted from the perspective of one of ordinary skill in the relevant art at the time of the invention. *Phillips*, 415 F.3d at 1313.

Claim construction starts with the claims, *id.* at 1312, and remains centered on the words of the claims throughout. *Interactive Gift Express, Inc. v. Compuserve, Inc.*, 256 F.3d 1323, 1331 (Fed. Cir. 2001). In the absence of an express intent to impart different meaning to claim terms, the terms are presumed to have their ordinary meaning. *Id.* Claims, however, must be read in view of the specification and prosecution history. Indeed, the specification is often "the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315.

B. "Acetohydroxy Acid Isomeroreductase Enzyme"

The above identified enzyme is recited in the engineered isobutanol biosynthetic pathway ("the pathway") claimed by Butamax. The patentees of the '188 and '889 patents offered a definition of this enzyme, *inter alia,* "to be used for the interpretation of the claims and the specification," to wit:

> The terms "acetohydroxy acid isomeroreductase" and "acetohydroxy acid reductoisomerace" are used interchangeably herein to refer to an enzyme that catalyzes the conversion of acetolactate to 2,3-dihydroxy- isovalerate using NADPH (reduced nicotinamide adenine dinucleotide phosphate) as an electron donor. Preferred acetohydroxy acid isomeroreductases are known by the EC number 1.1.1.86 and sequences are available from a vast array of microorganisms . . . .

('188 patent, 7:12-13, 35-42; '889 patent, 6:52-53, 7:8-15) Despite being a defined term, the parties dispute how persons of skill in the art would interpret the language used by the patentees, more specifically, whether those of skill in the art would include

within the scope of this definition enzymes that use either NADH or NADPH or both as a cofactor in the recited catalytic conversion.

Butamax suggests that a broad construction is most consistent with the intrinsic evidence and skill in the art, namely, "an enzyme that is structurally similar to acetohydroxy acid isomeroreductase or ketol acid reductoisomerase ["KARI"] enzymes[1] known by the EC number 1.1.1.86[2] and that converts acetolactate to 2,3-dihydroxyisovalerate." (D.I. 492 at 9) Under this construction, to determine whether an enzyme literally meets the claim term, a skilled artisan would: (1) compare the enzyme's amino acid sequence to the sequences of known KARI enzymes having EC number 1.1.1.86 (D.I. 492 at 10; D.I. 494 at ¶ 45); and (2) test the enzyme for activity using a standard KARI assay, e.g., the assay described in a 1969 reference by Arfin & Umbarger[3] (D.I. 492 at 10; D.I. 495 at ¶¶ 41-43). According to Butamax, "[t]his two prong analysis, consistent with the intrinsic evidence, allows a skilled artisan to come to a conclusion that an enzyme literally meets the KARI claim element." (D.I. 492 at 10) With respect to the characterization in the specification relating to cofactor NADPH, Butamax explains that, because it was well known in 2005 and 2006 that KARI

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[1]According to Butamax, "[t]he parties agree that 'acetohydroxy acid isomeroreductase' is synonymous with ketol acid isomeroreductase (KARI) and describes a class of enzymes that catalyzes the conversion of acetolactate (AL) to 2,3-dihydroxyisovalerate (DHIV)." (D.I. 492 at 9)

[2]The parties also agree that "EC number 1.1.1.86" refers to an "Enzyme Commission" number. (D.I. 492 at 9)

[3]"Arfin & Umbarger" is Stuart M. Arfin and H. Edwin Umbarger, *Purification and Properties of the Acetohydroxy Acid Isomeroreductase of* Salmonella typhimurium, 244(5) J. Biological Chemistry, 1118 (1969).

enzymes can use either NADPH or NADH as an electron donor (D.I. 494 at ¶ 36[4]), a construction limited to enzymes that will use solely NADPH is inappropriate without strong evidence of a clear intent to redefine the term narrowly, or an unambiguous disavowal of the full scope of the claim term.

Gevo's proposed construction is more narrow, that is, "an enzyme which catalyzes the conversion of acetolactate to 2,3-dihydroxyisovalerate and that is solely NADPH-dependent (as opposed to NADH-dependent or NADH and NADPH-dependent), having the EC number 1.1.1.86." (D.I. 535 at 7) According to Gevo, its construction is most consistent with the intrinsic record, given that the patentees specifically included within its definition of "acetoydroxy acid isomeroreductase," EC nomenclature and the use of NADPH as an electron donor, and clearly knew how to describe the use of both NADH and NADPH as cofactors, as they did elsewhere in the specification. (D.I. 535)

1. Intrinsic record

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[4]Dr. Rabinowitz, one of Butamax's experts, avers that,

> [w]here the only cofactor in the environment is NADPH, such as in the Arfin & Umbarger assay, a KARI will use that cofactor exclusively because it is the only one present. Likewise, in a system where the only cofactor in the environment is NADH, that cofactor will be used exclusively. In environments like living yeast cells, both cofactors are present in varying concentrations. Therefore, in such an environment, after each catalytic cycle, when the enzyme needs to bind another cofactor molecule, it will bind either NADPH or NADH. Which cofactor becomes bound at any one instance is random, but statistically both the concentration of the cofactor and the K_m for the cofactor will determine the aggregate cofactor binding.

(D.I. 494 at ¶ 36)

a. Prosecution history[5]

Claims 1, 4-8, 15-31 and 38 of the '188 patent were rejected by the examiner as failing to comply with the written description requirement, 35 U.S.C. § 112, first paragraph. (D.I. 508 at BJA 1482) It was the examiner's position that, while the specification described a genus of polypeptides catalyzing the reactions described in the pathway, the specification did not describe "any structural features, amino acid sequences, and/or biological functions that are commonly possessed by members of each claimed genus." (*Id.* at BJA1484) The specification also failed to disclose "a representative number of species of each claimed genus, which includes many members with widely differing structural, chemical, and biological functions. There is no recognized correlation between any structure and catalytic activity of conversion of the substrates to products as recited in parts i) - v)." (*Id.*)

The patentees responded by amending claim 1 "to an isobutanol producing host cell comprising at least one nucleic acid molecule that encodes the enzymes listed in claim 1 **as now further limited to those enzymes possessing a specific Enzyme Commission (EC) number to the fourth level.** It is well known in the art that the Enzyme Commission numbering system categorizes enzymes based on the reactions they are able to perform. An enzyme classed with an EC number to the fourth level is discretely and specifically classified on the basis of its function." (*Id.* at BJA1653 (emphasis added)) The patentees further disclosed a method that was "able to

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[5]The prosecution history for the '188 and '889 patents (D.I. 505-511) substantially track each other vis a vis the term in dispute. Therefore, the court will limit its references to the prosecution history of the '188 patent.

discriminate between enzymes assigned to different EC numbers exhibiting distinct functions," thus "indicating a correlation between structural elements of enzyme binding pockets and their functional classification by EC number." (*Id.* at BJA1654) In sum, the patentees submitted that "the specific guidance relating to the structure and physiochemical properties of enzymes that may be used in the invention [were] provided in the EC number of each enzyme." (*Id.* at BJA1656)

The examiner also rejected the application on enablement grounds. In this regard, the patentees responded that "[a] patent need not teach, and preferably omits, what is well known in the art. . . Thus a claim is enabled if the specification **in combination** with what is well known in the art permits the skilled person to make and use the invention without undue experimentation." (*Id.* at BJA1701-2) To illustrate their point, the patentees referred the examiner to a publicly available database and explained that, "[u]sing the BRENDA database, the skilled person, searching for the EC number for[, e.g.,] acetolactate synthase . . . would find corresponding enzymes catalyzing the conversion of pyruvate to acetolactate from 39 organisms. These polypeptides and the genes encoding them can be obtained from the recited organisms by methods well known in the art and without any excessive screening or additional guidance and used in the present invention." (*Id.* at BJA1702)

The '188 patent ultimately issued on December 14, 2010. As noted by the patentees in the prosecution history, claim 1 was amended to "limit the enzyme terms to their corresponding EC numbers." (*Id.* at BJA1652)

b. Specification

In addition to defining the enzymes of the pathway by their known EC numbers, the patentees added cofactor information to some of the definitions, including the one in dispute. For example, in defining the term "branched-chain alcohol dehydrogenase," the patentees instructed that "[p]referred branched-chain alcohol dehydrogenases are known by the EC number 1.1.1.265, but may also be classified under other alcohol dehydrogenases (specifically, EC 1.1.1.1 or 1.1.1.2)," and then noted that "[t]hese enzymes utilize NADH . . . and/or NADPH as electron donor." ('188 patent, 8:9-16; '889 patent, 7:49-56) Likewise, in defining the term "acylating aldehyde dehydrogenase," the patentees referred to an enzyme that "catalyzes the conversion of isobutyryl-CcA to isobutyraldehyde, using either NADH or NADPH as electron donor," with "preferred" enzymes "known by the EC numbers 1.2.1.10 and 1.2.1.57." ('188 patent, 8:44-48; '889 patent, 8:17-21) In addition, in defining the term "valine dehydrogenase," the patentees referred "to an enzyme that catalyzes the conversion of α-ketoisovalerate to L-valine using NAD(P)H as electron donor," instructing that "preferred" enzymes "are known by the EC numbers 1.4.1.8 and 1.4.1.9." ('188 patent, 9:9-11; '889 patent, 8:49-51) Finally, the patentees defined the term "branched-chain keto acid dehydrogenase" as "an enzyme that catalyzes the conversion of α-ketoisovalerate to isobutyryl-CoA (isobutrl-coenzyme A), using NAD^+ (nicotinamide adenine dinucleotide) as electron acceptor," instructing that "preferred" enzymes are "known by the EC number 1.2.4.4." ('188 patent, 8:25-29; '889 patent, 7:65-8:3)

Claim 1 of the '188 patent includes the EC nomenclature for the enzymes of the pathway; claim 1 of the '889 patent does not. ('188 patent, 335:21-45; '889 patent, 325:16-42) Dependent claim 14 of the '889 patent refers to the method of claim 1, with

the further limitation that "one or more enzymes of said engineered isobutanol biosynthetic pathway uses NADH as an electron donor." ('889 patent, 326:37-39)

2. Extrinsic evidence[6]

The term "cofactor" is generally understood to refer to an organic molecule that is required for certain enzymatically catalyzed reactions to proceed. Cofactors bind to enzymes as substrates of the enzymes that rely on them and are converted to products of the enzymatic reaction after it is completed. NADH and NADPH are two important and distinct cofactors that are also substrates. These cofactors act as electron donors and, in their oxidized forms (NAD^+ and $NADP^+$), as electron acceptors, respectively, in oxidation or reduction reactions. Enzymes that depend on them for catalytic activity are frequently termed NADH- or NADPH-dependent. (D.I. 537 at ¶¶ 8, 9)

NADH and NADPH have distinct chemical structures, with NADPH containing an additional phosphate group. This extra phosphate group allows NADPH "to be recognized selectively by the enzymes involved in biosynthesis;" thus, "'despite their close chemical resemblance,' NADH and NADPH are 'not metabolically interchangeable.'" (*Id.* at ¶¶ 4, 12 (citations omitted)) To put the point another way, "[t]he difference between NADH and NADPH is trivial in chemical terms, but it is crucial for their distinctive functions." (*Id.* at ¶ 11 (citation omitted))

"As of October 26, 2005, all natural KARI enzymes were known to be NADPH-

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[6]The court recognizes that extrinsic evidence generally is not considered in the claim construction exercise. Under the circumstances at bar, however, where the parties are disputing how those of skill in the art would interpret the definition provided by the patentees, the court finds it instructive, if not imperative, to consider expert testimony and the scientific literature referenced in the patent to illuminate the disputed language.

dependent." (D.I. 537 at ¶ 40) Although "the limits of biology virtually guarantee that all KARI enzymes will have at least some ancillary activity with both cofactors," a person of ordinary skill in the art would understand that an enzyme that "uses NADPH" or that "uses NADH" is "NADPH-dependent" or "NADH-dependent", respectively. (*Id.* at ¶ 58)

The EC enzyme classification system was developed in the 1950s to provide international standards of nomenclature. According to the "second general principle" of the EC classification system, "enzymes are principally classified and named according to the reaction they catalyse. The chemical reaction catalysed is the specific property that distinguishes one enzyme from another, and it is logical to use it as the basis for the classification and naming of enzymes." (D.I. 496, ex. A at 5) Relevant to the dispute at bar is Rule 18 of the EC nomenclature, which states that, "[f]or oxidoreductases using NAD^+ or $NADP^+$, the coenzyme should always be named as the acceptor[[7]] . . . Where the enzyme can use either coenzyme, this should be indicated by writing $NAD(P)^+$." (D.I. 496, ex. A at 18) Although some enzymes are classified based on their cofactor selectivity,[8] no unique EC numbers have been assigned to EC 1.1.1.86 to reflect this feature.

Examining EC 1.1.1.86, the chemical reaction that distinguishes this class of

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[7]With an exception apparently not applicable here.

[8]*See, e.g.*, the EC nomenclature for some of the enzymes defined in the patents-in-suit, to wit: "EC 1.1.1.1 - alcohol dehydrogenase" (which only describes reactions using NAD+) compared with "EC 1.1.1.2 - alcohol dehydrogenase (NADP+)" (which only describes reactions using NADP+); and "EC 1.4.1.8 - valine dehydrogenase (NADP+)" (which only describes reactions using NADPH) compared with "EC 1.4.1.9 - leucine dehydrogenase" (which only describes reactions using NADH). (http://www.brenda-enzymes.info)

enzymes is described as "(*R*)-2,3-dihydroxy-3-methylbutanoate + $NADP^+$ = (*S*)-2-hydroxy-2-methyl-3-oxobutanoate + NADPH + H^+." (D.I. 496, ex. C) The IUBMB[9] Enzyme Nomenclature also includes four references[10] and links to other databases. With respect to the listed references: (1) Arfin & Umbarger, which describes a standard assay to identify a KARI enzyme in an environment where AL and NADPH are present (*id.,* ex. E; D.I. 492 at 10-11); (2) Hill, which studied the synthesis, configuration and enzymatic specificity of intermediates involved in the biosynthesis of isoleucine and valine, notes that "[a]ssays were performed by measuring the rate at which NADPH was oxidized, as described previously by Arfin & Umbarger" (D.I. 496, ex. F at 175-76, 181); (3) Kiritani, which sought to characterize the reductoisomerase involved in the isoleucine-valine pathway of *Neurospora crassa*, includes the observation that "NADPH is required for enzymatic activity, and NADH does not substitute" (D.I. 496, ex. G at 2047-48); and (4) Satyanarayana, which studied the properties of a reductoisomerase involved in the synthesis of valine and isoleucine in plants, used TPNH,[11] and states that no α-keto-β-hydroxy acids could be detected when "TPNH was omitted from the standard assay mixture" (*id.*, ex. H at 380-81, 387).

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[9]The International Union of Biochemistry and Molecular Biology. (D.I. 495 at ¶17)

[10]"Hill" is Richard K. Hill and Seiji Sawada, *Stereochemistry of Valine and Isoleucine Biosynthesis*, 8 Bioorganic Chemistry, 175 (1979). "Kiritani" is Kiritani, et al., *The Reductoisomerase of* Neurospora crassa, 241(9) J. Biological Chemistry, 2047 (1966). "Satyanarayana" is T. Satyanarayana and A. N. Radhakrishnan, *Biosynthesis of Valine and Isoleucine in plants*, 110 Biochimica et Biophysica Acta, 380 (1965).

[11]TPNH is an older notation form of NADPH. *See e.g.* http://pubchem.ncbi.nlm.nih.gov/.

In looking at the enzyme entries for EC 1.1.1.86 found in the listed databases, one finds the following: (1) the ExPASy database entry describes the reaction catalyzed as one using NADPH (D.I. 497, ex. FF); (2) the KEGG database entry describes the reaction, the substrate, and the product in relation to NADPH or NADP+ (*id.*, ex. GG); (3) the PDB database entry describes reactions involving NADPH and NADP(+)[12] (*id.*, ex. HH); and (4) the BRENDA database entry likewise describes the reaction in relation to NADPH (*id.*, ex. D at 1).

Unlike the other databases identified in the IUBMB Enzyme Nomenclature, the BRENDA database includes information about specific activity, substrates, products, and organisms, with commentaries and multiple references to literature. In the 43 pages of information contained on the BRENDA database for EC 1.1.1.86, NADH is mentioned in only 16 entries, all of which refer to one or more of only five literature references.[13] (*Id.*, ex. D at 13-14, 22, 25, 28, 39-40) The five literature references are:

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[12]The PDB database also includes the following diagram:

EC 1.-.-.- Oxidoreductases.

EC 1.1.-.- Acting on the CH-OH group of donors.

EC 1.1.1.- With NAD(+) or NADP(+) as acceptor.

EC 1.1.1.86 Ketol-acid reductoisomerase.

[13]"Dumas (1989)" is Renaud Dumas et al., *Purification and Characterization of Acetohydroxyacid Reductoisomerase from Spinach Chloroplasts*, 262 Biochem. J., 971 (1989). "Dumas (1992)" is Renaud Dumas et al., *Isolation and Kinetic Properties of Acetohydroxy Acid Isomeroreductase from Spinach (*Spinacia oleracea*) Chloroplasts Overexpressed in* Escherichia coli, 288 Biochem. J., 865 (1992). "Rane" is Madhavi J. Rane and K. C. Calvo, *Reversal of the Nucleotide Specificity of Ketol Acid Reductoisomerase by Site-Directed Mutagenesis Identifies the NADPH Binding Site*, 338(1) Archives Biochemistry and Biophysics, 83 (1997).

(1) Arfin & Umbarger (reference 639169), as described above; (2) Kiritani (reference 639171), as described above; (3) Dumas (1989) (reference 639176), which includes the observation that "[t]he enzyme also utilized NADH as electron donor," but describes the reaction as an "NADPH-dependent reduction" and goes on to analyze how the enzyme was regulated by the NADPH/$NADP^+$ ratio (D.I. 497, ex. AA at 971, 974-975); (4) Dumas (1992) (reference 639176), which reiterates the earlier observation that "the over-expressed enzyme was able to use NADH as an electron donor," nevertheless, "the plant enzyme displays a very high selectivity for NADPH" (D.I. 538, ex. X at 870, 873); and (5) Rane (reference 639183), which started with the stated goal of "identify[ing] the positively charged amino acid(s) that confer NADPH specificity on KARI," and found that by altering four amino acids and constructing a "quadruplet mutant," "the specificity constants for NADH and NADPH are almost exactly reversed in the mutant relative to the wild type," i.e., the "mutant was changed from being a NADPH-specific dehydrogenase into a NADH specific enzyme" (D.I. 497, ex. BB).

In connection with the argument posed by Butamax that the specification "lists 'preferred' KARIs, denoted by EC 1.1.1.86, that have **significant activity with NADH,**" (D.I. 492 at 11 (emphasis added)), the one KARI enzyme identified in this regard is the *Methanococcus maripaludis* KARI ('188 patent, 7:46-47; '889 patent, 7:19-20) and the analysis of such KARI enzyme in a single reference, R. Xing. & W. Whitman, *Characterization of Enzymes of the Branched-Chain Amino Acid Biosynthetic Pathway in* Methanococcus *spp*, 173(6) J. Bacteriology 2086-2092 (1991). (D.I. 496, ex. K; *see* D.I. 492 at 11; D.I. 493 at ¶ 34; D.I. 494 at ¶¶ 39-40; D.I. 495 at ¶ 48) The authors of

the reference observe that, "[w]hile the eubacterial and eucaryotic AAIRs are NADPH specific, NADH supported 60% of the methanococcal activity obtained with NADPH." (D.I.496, ex. K at 2089) There is neither a reference nor data noted to support this assertion.

3. Analysis

The court starts with the premise that the claims and specification of a patent serve a public notice function, and that patentees who choose to provide definitions should be especially mindful of being their own lexicographers. *See, e.g., Johnson & Johnston Associates Inc. v. R.E. Service Co., Inc.*, 285 F.3d 1046, 1052 (Fed. Cir. 2002) (citing *Mahn v. Harwood*, 112 U.S. 354, 361 (1884)) (claims give notice to the public of the scope of the patent); *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994) (patentee choosing to define terms must do so "with reasonable clarity, deliberateness, and precision"). In this case, the patentees choose to define the KARI enzyme not only by reference to its EC classification, but by its "use" of NADPH. Having reviewed the scientific literature referenced through the patent's definitional language, the court finds the expert opinions proffered by Gevo (and, therefore, Gevo's proposed construction) to be more consistent with the intrinsic record.

In this regard, the scientific references almost exclusively characterize KARI enzymes as NADPH-dependent. Of the two references relied on by Butamax to support the use of NADH by KARI enzymes,[14] one (Xing) included a single conclusory sentence with no data or other literature references to support it, and the other (Rane)

[14]By "use," the court refers not to ancillary activity, but that the enzyme is NADH- or NADPH-dependent.

described having to construct a "quadruplet mutant" in order to change a KARI enzyme from being NADPH-dependent to being NADH-dependent.

Even if the court were to accept the proposition that those of skill in the art recognized in 2005 that the KARI enzyme known by EC number 1.1.1.86 could use NADH and/or NADPH as an electron donor, consistent with Butamax's position in this dispute, the question remains why the patentees choose then to include more limiting language in their definition. Butamax responds by arguing that NADPH was simply a known tool for identifying a KARI enzyme (referencing the Arfin & Umbarger standard assay), and co-factor usage was not meant to be a limiting physiochemical property of the enzyme.

The court declines, however, to make superfluous the patentees' description of the very reaction that is the defining characteristic of the KARI enzyme. In light of the record,[15] the patentees' definition of "acethydroxy acid isomeroreductase enzyme" simply reflects the state of the art, that is, that the KARI enzyme known by the EC number 1.1.1.86 was generally understood to be NADPH-dependent. That dependent claim 14 of the '889 patent calls out use of NADH is of no moment in this analysis, given that more than one of the enzymes of the claimed pathway were defined by the patentees as using NADH as an electron donor. ('889 patent, 7:54-56, 7:67-8:1, 8:19, 51)

4. Conclusion

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[15]Including, but not limited to, the fact that NADH and NADPH are different in terms of structure and function and, even if (or especially if) it was well known in the art that KARI enzymes could "use" either NADH or NADPH or both, the patentees knew how to describe that and choose not to.

For the reasons stated above, the court concludes that a person of ordinary skill in the art would understand "acetohydroxy acid isomeroreductase" to be "an enzyme known by the EC number 1.1.1.86 that catalyzes the conversion of acetolactate to 2,3-dihydroxyisovalerate and is NADPH-dependent."

C. Other Terms of the '889 Patent

1. "[A] recombinant yeast micoorganism expressing an engineered isobutanol biosynthetic pathway"

The court construes this term to mean "a recombinant yeast microorganism that is genetically transformed such that it expresses the five enzymes that form the biosynthetic pathway described hereafter for the production of isobutanol, wherein one or more of those enzymes is recombinantly expressed."

Butamax does not contend that all five enzymes in the "engineered isobutanol biosynthetic pathway" must be recombinantly expressed and Gevo asserts that "the patent contemplates engineered pathways where only one or more of the enzymes are recombinantly expressed." (D.I. 492 at 26; D.I. 535 at 27) The court's construction resolves any ambiguity in this regards. According to Butamax, "[t]he parties' only apparent substantive dispute regarding this term is whether it should be construed to require carbon flow through pathway steps a-e recited later in the claim." (D.I. 552 at 12) Gevo argues that Butamax's construction is ambiguous and that "the patent recites several different pathways for isobutanol production." (D.I. 535 at 28) The court finds that the remaining language of the claim resolves this dispute. In other words, the entire phrase "a recombinant yeast micoorganism expressing an engineered isobutanol

biosynthetic pathway . . . **wherein said pathway comprises the following substrate to product conversions**" instructs that the "engineered isobutanol biosynthetic pathway" is in fact the pathway described in the following steps a-e. ('889 patent, 325:19-22 (emphasis added))

2. "([P]athway step a);...(pathway step b);...," etc.

The court construes this term to mean "the pathway steps a-e are contiguous steps such that the product of step a is the substrate for step b; the product of step b is the substrate for step c; etc." The court recognizes that the term "comprising" recited in the introductory language "raises a presumption that the list of elements is nonexclusive." *Dippin' Dots, Inc. v. Mosey,* 476 F.3d 1337, 1343 (Fed. Cir. 2007). However, the court agrees with Butamax that the intrinsic evidence demonstrates the patentees' intent that the addition of intermediate steps to the preferred claim 1 pathway forms a different pathway that is outside the scope of the claim and that the claim's use of "comprising" reflects that the claimed pathway can be used as part of a larger process, and additional steps might be performed before or after without avoiding infringement. (D.I. 492 at 28-29) This construction is not inconsistent with *Dippin' Dots*, wherein the Federal Circuit declares that the enumerated steps "must . . . all be practiced as recited in the claim for a process to infringe." *Id.*

3. "The microorganism produces isobutanol as a single product"

The parties agree that any fermentation process produces more than one single product.[16] (D.I. 552 at 15) Butamax reasons that one skilled in the art would

[16]The court notes that Gevo acknowledges that any fermentation process produces more than one single product in its later filings. (D.I. 623 at 54; *see infra* part

understand this term to mean producing "predominantly one product." (D.I. 552 at 15) This reasoning is consistent with distinguishing the production of isobutanol as a primary product with production of by-products or as part of a mixture. The court construes this term to mean "[t]he microorganism produces isobutanol without substantial amounts of other fermentation products."

IV. STANDARDS OF REVIEW

A. Summary Judgment

"The court shall grant summary judgment if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). The moving party bears the burden of demonstrating the absence of a genuine issue of material fact. *Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 415 U.S. 574, 586 n.10 (1986). A party asserting that a fact cannot be—or, alternatively, is—genuinely disputed must support the assertion either by citing to "particular parts of materials in the record, including depositions, documents, electronically stored information, affidavits or declarations, stipulations (including those made for the purposes of the motions only), admissions, interrogatory answers, or other materials," or by "showing that the materials cited do not establish the absence or presence of a genuine dispute, or that an adverse party cannot produce admissible evidence to support the fact." Fed. R. Civ. P. 56(c)(1)(A) & (B). If the moving party has carried its burden, the nonmovant must then "come forward with specific facts showing that there is a genuine issue for trial." *Matsushita*, 415 U.S. at 587 (internal quotation

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IV.B.3.a.)

marks omitted). The court will "draw all reasonable inferences in favor of the nonmoving party, and it may not make credibility determinations or weigh the evidence." *Reeves v. Sanderson Plumbing Prods., Inc.*, 530 U.S. 133, 150 (2000).

To defeat a motion for summary judgment, the non-moving party must "do more than simply show that there is some metaphysical doubt as to the material facts." *Matsushita*, 475 U.S. at 586-87; *see also Podohnik v. U.S. Postal Service*, 409 F.3d 584, 594 (3d Cir. 2005) (stating party opposing summary judgment "must present more than just bare assertions, conclusory allegations or suspicions to show the existence of a genuine issue") (internal quotation marks omitted). Although the "mere existence of some alleged factual dispute between the parties will not defeat an otherwise properly supported motion for summary judgment," a factual dispute is genuine where "the evidence is such that a reasonable jury could return a verdict for the nonmoving party." *Anderson v. Liberty Lobby, Inc.*, 411 U.S. 242, 247-48 (1986). "If the evidence is merely colorable, or is not significantly probative, summary judgment may be granted." *Id.* at 249-50 (internal citations omitted); *see also Celotex Corp. v. Catrett*, 411 U.S. 317, 322 (1986) (stating entry of summary judgment is mandated "against a party who fails to make a showing sufficient to establish the existence of an element essential to that party's case, and on which that party will bear the burden of proof at trial").

B. Infringement

A patent is infringed when a person "without authority makes, uses or sells any patented invention, within the United States . . . during the term of the patent." 35 U.S.C. § 271(a). A two-step analysis is employed in making an infringement

determination. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995). First, the court must construe the asserted claims to ascertain their meaning and scope. *See id*. Construction of the claims is a question of law subject to de novo review. *See Cybor Corp. v. FAS Techs.*, 138 F.3d 1448, 1454 (Fed. Cir. 1998). The trier of fact must then compare the properly construed claims with the accused infringing product. *See Markman*, 52 F.3d at 976. This second step is a question of fact. *See Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998).

"Direct infringement requires a party to perform each and every step or element of a claimed method or product." *BMC Res., Inc. v. Paymentech, L.P.*, 498 F.3d 1373, 1378 (Fed. Cir. 2007), *overruled on other grounds by* 692 F.3d 1301 (Fed. Cir. 2012). "If any claim limitation is absent from the accused device, there is no literal infringement as a matter of law." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000). If an accused product does not infringe an independent claim, it also does not infringe any claim depending thereon. *See Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989). However, "[o]ne may infringe an independent claim and not infringe a claim dependent on that claim." *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1359 (Fed. Cir. 2007) (quoting *Wahpeton Canvas*, 870 F.2d at 1552) (internal quotations omitted). A product that does not literally infringe a patent claim may still infringe under the doctrine of equivalents if the differences between an individual limitation of the claimed invention and an element of the accused product are insubstantial. *See Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 24, 117 S. Ct. 1040, 137 L. Ed. 2d 146 (1997). The patent

owner has the burden of proving infringement and must meet its burden by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988) (citations omitted).

When an accused infringer moves for summary judgment of non-infringement, such relief may be granted only if one or more limitations of the claim in question does not read on an element of the accused product, either literally or under the doctrine of equivalents. *See Chimie v. PPG Indus., Inc.*, 402 F.3d 1371, 1376 (Fed. Cir. 2005); *see also TechSearch, L.L.C. v. Intel Corp.*, 286 F.3d 1360, 1369 (Fed. Cir. 2002) ("Summary judgment of noninfringement is ... appropriate where the patent owner's proof is deficient in meeting an essential part of the legal standard for infringement, because such failure will render all other facts immaterial."). Thus, summary judgment of non-infringement can only be granted if, after viewing the facts in the light most favorable to the non-movant, there is no genuine issue as to whether the accused product is covered by the claims (as construed by the court). *See Pitney Bowes, Inc. v. Hewlett–Packard Co.*, 182 F.3d 1298, 1304 (Fed. Cir. 1999).

For there to be infringement under the doctrine of equivalents, the accused product or process must embody every limitation of a claim, either literally or by an equivalent. *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 41 (1997). An element is equivalent if the differences between the element and the claim limitation are "insubstantial." *Zelinski v. Brunswick Corp.*, 185 F.3d 1311, 1316 (Fed. Cir. 1999). One test used to determine "insubstantiality" is whether the element performs substantially the same function in substantially the same way to obtain substantially the

same result as the claim limitation. *See Graver Tank & Mfg. Co. v. Linde Air Products Co.*, 339 U.S. 605, 608 (1950). This test is commonly referred to as the "function-way-result" test. The mere showing that an accused device is equivalent overall to the claimed invention is insufficient to establish infringement under the doctrine of equivalents. The patent owner has the burden of proving infringement under the doctrine of equivalents and must meet its burden by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988) (citations omitted).

The doctrine of equivalents is limited by the doctrine of prosecution history estoppel. In *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 535 U.S. 722 (2002), the Supreme Court stated:

> Prosecution history estoppel ensures that the doctrine of equivalents remains tied to its underlying purpose. Where the original application once embraced the purported equivalent but the patentee narrowed his claims to obtain the patent or to protect its validity, the patentee cannot assert that he lacked the words to describe the subject matter in question. The doctrine of equivalents is premised on language's inability to capture the essence of innovation, but a prior application describing the precise element at issue undercuts that premise. In that instance the prosecution history has established that the inventor turned his attention to the subject matter in question, knew the words for both the broader and narrower claim, and affirmatively chose the latter.

Id. at 734-735. In other words, the prosecution history of a patent, as the public record of the patent proceedings, serves the important function of identifying the boundaries of the patentee's property rights. Once a patentee has narrowed the scope of a patent claim as a condition of receiving a patent, the patentee may not recapture the subject

matter surrendered. In order for prosecution history estoppel to apply, however, there must be a deliberate and express surrender of subject matter. *See Southwall Tech., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1580 (Fed. Cir. 1995).

Once a court has determined that prosecution history estoppel applies, it must determine the scope of the estoppel. *See id.* at 1580. This requires an objective examination into the reason for and nature of the surrendered subject matter. *Id.*; *see also Augustine Med., Inc. v. Gaymar Indus., Inc.*, 181 F.3d 1291, 1299 (Fed. Cir. 1999). If one of ordinary skill in the art would consider the accused product to be surrendered subject matter, then the doctrine of equivalents cannot be used to claim infringement by the accused product; i.e., prosecution history estoppel necessarily applies. *Augustine Med.*, 181 F.3d at 1298. In addition, a "patentee may not assert coverage of a 'trivial' variation of the distinguished prior art feature as an equivalent." *Id.* at 1299 (quoting *Litton Sys., Inc. v. Honeywell, Inc.*, 140 F.3d 1449, 1454 (Fed. Cir. 1998)).

C. Invalidity

1. Anticipation

An anticipation inquiry involves two steps. First, the court must construe the claims of the patent in suit as a matter of law. *Key Pharms. v. Hercon Labs Corp.*, 161 F.3d 709, 714 (Fed. Cir. 1998). Second, the finder of fact must compare the construed claims against the prior art. *Id.* A finding of anticipation will invalidate the patent. *Applied Med. Res. Corp. v. U.S. Surgical Corp.*, 147 F.3d 1374, 1378 (Fed. Cir. 1998).

Under 35 U.S.C. § 102(b), "[a] person shall be entitled to a patent unless the invention was patented or described in a printed publication in this or a foreign country .

. . more than one year prior to the date of the application for patent in the United States." The Federal Circuit has stated that "[t]here must be no difference between the claimed invention and the referenced disclosure, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic & Research Found. v. Genentech, Inc.,* 927 F.2d 1565, 1576 (Fed. Cir.1991). In determining whether a patented invention is explicitly anticipated, the claims are read in the context of the patent specification in which they arise and in which the invention is described. *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply, Inc.*, 45 F.3d 1550, 1554 (Fed. Cir. 1995). The prosecution history and the prior art may be consulted if needed to impart clarity or to avoid ambiguity in ascertaining whether the invention is novel or was previously known in the art. *Id.* The prior art need not be ipsissimis verbis (i.e., use identical words as those recited in the claims) to be anticipating. *Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984).

A prior art reference also may anticipate without explicitly disclosing a feature of the claimed invention if that missing characteristic is inherently present in the single anticipating reference. *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991). The Federal Circuit has explained that an inherent limitation is one that is necessarily present and not one that may be established by probabilities or possibilities. *Id.* That is, "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* The Federal Circuit also has observed that "[i]nherency operates to anticipate entire inventions as well as single limitations within an invention." *Schering Corp. V. Geneva Pharms. Inc.*, 339 F.3d 1373, 1380 (Fed. Cir.

2003). Moreover, recognition of an inherent limitation by a person of ordinary skill in the art before the critical date is not required to establish inherent anticipation. *Id.* at 1377.

2. Obviousness

"A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a question of law, which depends on underlying factual inquiries.

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. Likewise, a defendant asserting obviousness in view of a combination of references has the burden to show that a person of ordinary skill in the relevant field had a reason to combine the elements in the manner claimed. *Id.* at 418-19. The Supreme Court has emphasized the need for courts to value "common sense" over "rigid preventative rules" in determining whether a motivation to combine existed.

Id. at 419-20. "[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. In addition to showing that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, a defendant must also demonstrate that "such a person would have had a reasonable expectation of success in doing so." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007).

A combination of prior art elements may have been "obvious to try" where there existed "a design need or market pressure to solve a problem and there [were] a finite number of identified, predictable solutions" to it, and the pursuit of the "known options within [a person of ordinary skill in the art's] technical grasp" leads to the anticipated success. *Id.* at 421. In this circumstance, "the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.* Federal Circuit precedent has also established that "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds," and that particular types of structural similarity can give rise to a case of prima facie obviousness. *Genetics Institute, LLC v. Novartis Vaccines and Diagnostics, Inc.*, 655 F.3d 1291, 1312 (Fed. Cir. 2011) (citing *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995)).

A court is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight bias." *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1079 (Fed. Cir. 2012). "Such secondary considerations as

commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966).

"Because patents are presumed to be valid, *see* 35 U.S.C. § 282, an alleged infringer seeking to invalidate a patent on obviousness grounds must establish its obviousness by facts supported by clear and convincing evidence." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 968 (Fed. Cir. 2006) (citation omitted). In conjunction with this burden, the Federal Circuit has explained that,

> [w]hen no prior art other than that which was considered by the PTO examiner is relied on by the attacker, he has the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents.

PowerOasis, Inc. v. T-Mobile USA, Inc., 522 F.3d 1299, 1304 (Fed. Cir. 2008) (quoting *Am. Hoist & Derrick Co. v. Sowa & Sons*, 725 F.2d 1350, 1359 (Fed. Cir. 1984)).

3. Written description

a. Indefiniteness

The definiteness requirement is rooted in § 112, ¶ 2, which provides that "the specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." "A determination of claim indefiniteness is a legal conclusion that is drawn from the court's

performance of its duty as the construer of patent claims." *Personalized Media Comm., LLC v. Int'l Trade Com'n*, 161 F.3d 696, 705 (Fed. Cir. 1998).

> Determining whether a claim is definite requires an analysis of whether one skilled in the art would understand the bounds of the claim when read in light of the specification . . . If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more.

Id. (citing *Miles Lab., Inc. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993)).

b. Enablement and written description

The statutory basis for the enablement and written description requirements, § 112 ¶1, provides in relevant part:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . . .

"The enablement requirement is met where one skilled in the art, having read the specification, could practice the invention without 'undue experimentation.'" *Streck, Inc. v. Research & Diagnostic Systems, Inc.*, 665 F.3d 1269, 1288 (Fed. Cir. 2012) (citation omitted). "While every aspect of a generic claim certainly need not have been carried out by the inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). The specification need not teach what is well known in the art. *Id.* (citing *Hybritech v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986)). A reasonable

amount of experimentation may be required, so long as such experimentation is not "undue." *ALZA Corp. v. Andrx Pharms., Inc.*, 603 F.3d 935, 940 (Fed. Cir. 2010).

"Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1378 (Fed. Cir. 2009) (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The Federal Circuit has provided several factors that may be utilized in determining whether a disclosure would require undue experimentation: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance disclosed in the patent; (3) the presence or absence of working examples in the patent; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability of the art; and (8) the breadth of the claims. *In re Wands*, 858 F.2d at 737. These factors are sometimes referred to as the "*Wands* factors." A court need not consider every one of the *Wands* factors in its analysis, rather, a court is only required to consider those factors relevant to the facts of the case. *See Streck, Inc.*, 655 F.3d at 1288 (citing *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991)).

The enablement requirement is a question of law based on underlying factual inquiries. *See Green Edge Enters., LLC v. Rubber Mulch Etc., LLC*, 620 F.3d 1287, 1298-99 (Fed. Cir. 2010) (citation omitted); *Wands*, 858 F.2d at 737. Enablement is determined as of the filing date of the patent application. *In re '318 Patent Infringement Litigation*, 583 F.3d 1317, 1323 (Fed. Cir. 2009) (citation omitted). The burden is on

one challenging validity to show, by clear and convincing evidence, that the specification is not enabling. *See Streck, Inc.*, 665 F.3d at 1288 (citation omitted).

A patent must also contain a written description of the invention. 35 U.S.C. § 112, ¶ 1. The written description requirement is separate and distinct from the enablement requirement. *See Ariad Pharms., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2011). It ensures that "the patentee had possession of the claimed invention at the time of the application, i.e., that the patentee invented what is claimed." *LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1344-45 (Fed. Cir. 2005). The Federal Circuit has stated that the relevant inquiry – "possession as shown in the disclosure" – is an "objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art. Based on that inquiry, the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed." *Ariad*, 598 F.3d at 1351.

This inquiry is a question of fact: "the level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Id.* (citation omitted). In this regard, Gevo must provide clear and convincing evidence that persons skilled in the art would not recognize in the disclosure a description of the claimed invention. *See PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1306-17 (Fed. Cir. 2008) (citation omitted). While compliance with the written description requirement is a question of fact, the issue is "amenable to summary judgment in cases where no reasonable fact finder could return a verdict for the non-moving party." *Id.* at 1307

(citing *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1072-73 (Fed. Cir. 2005)).

V. DISCUSSION

A. Infringement

The court starts its infringement analysis of claim 1 of both patents-in-suit with the term "acetohydroxy acid isomeroreductase," construed by the court as "NADPH-dependent." Butamax contends that Gevo's lead strains are similar to KARIs having E.C. number 1.1.1.86 and catalyze the AL to DHIV conversion.[17] (D.I. 596 at 18, 20) Butamax makes the following usage arguments in light of its alternative claim construction, which includes "using NADPH as an electron donor."[18] (D.I. 596 at 31; D.I. 648 at 30) Gevo's lead strains "use NADPH at values similar to or greater than several wild-type KARIs from other bacteria." (D.I. 596 at 20 (emphasis omitted); D.I. 648 at 30) For instance, the patents-in-suit identify a specific activity of 0.026 units/mg

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[17]Butamax specifically references Gevo's strains P2D1A and SE26E6. (D.I. 596 at 17) Butamax's experts analyzed the P2D1A1 enzyme and found that the "sequence is 99% identical to several . . . KARI enzymes . . . having E.C. number 1.1.1.86." (*Id.* at 19)

[18]Although the court is most interested in Butamax's arguments under a "NADH-dependent" construction, Butamax's usage arguments are considered for completeness. In its opening brief, Butamax does not address infringement under Gevo's proposed construction. (D.I. 596) Butamax responded to Gevo's summary judgment motion of non-infringement, argued primarily from a standpoint that Gevo's claim construction of acetohydroxy acid reductoisomerase as "solely NADPH dependent" is correct (D.I. 611), by arguing for its proposed claim construction (D.I. 648). Butamax chooses to offer the following unsupported argument if Gevo's claim construction is adopted: "Even under Gevo's claim construction, there are genuine issues of material fact precluding summary judgment of non-infringement, as both parties' experts agree a KARI's use of NADPH is insubstantially different than use of NADH." (D.I. 648 at 32)

with an enzyme having KARI activity.[19] (D.I. 648 at 30 (citing '889 patent, 35:2-9 and '188 patent, 39:5-10)) Butamax then compares this specific activity to several values disclosed in Gevo's patents and published data, concluding that the data "prove[s the] activity with NADPH exceeds the 0.026 units/mg disclosed in the Butamax patents."[20] (D.I. 648 at 30 (emphasis omitted)) Butamax asserts "that P2D1A1 and SE26E6 have statistically significant activity with NADPH, which follows a dose response," based on its expert's experiments.[21] (D.I. 596 at 21) Butamax further argues that Gevo's KARI enzymes "can use NADH or NADPH, as they have roughly equivalent specific activity with use of either cofactor." (D.I. 648 at 31) To support this statement, Butamax cites to Gevo's published data showing a 6 to 1 and 8 to 1 preference for NADH to NADPH for SE26E6 and P2D1A1 strains, respectively, determined using specific activities. (D.I. 648 at 31) Butamax concludes that this difference is not enough to define Gevo's KARIs as NADH-dependent, comparing the difference to Dr. Kirsh's "gray area" in cofactor usage.[22] (D.I. 648 at 31)

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[19]For this proposition, Butamax cites to example 10, which describes a method for cloning and expression of acetohydroxy acid reductoisomerase in *E. coli.* The activity of enzyme was then measured in the cell free extracts. ('889 patent, 34:45-35:9 and '188 patent, 38:45-39:10) "Three hours after induction with IPTG, an acetohydroxy acid reductoisomerase activity of 0.026 units/mg was detected." ('889 patent, 35:2-9 and '188 patent, 39:5-10)

[20]Butamax cites a Gevo patent indicating specific activities of 0.15 U/mg and 0.1 U/mg for P2D1A1 and SE26E6 respectively. (D.I. 648 at 30)

[21]Butamax's expert, Dr. Brown, used assays as described by Arfin & Umbarger. (D.I. 596 at 21; D.I. 648 at 31 & n.16; D.I. 649, ex. MMMM at ¶¶ 13-19 and NNNN at 166-71)

[22]Gevo's expert, Dr. Kirsh, testified that an enzyme that "use[d] exclusively or nearly exclusively NADH as opposed to NADPH" would show usage "at some level

In response, Gevo asserts that its strains are NADH-dependent and do not infringe Butamax's patents. (D.I. 611 at 34-39) Citing to the same set of published data as Butamax, but relying on kinetic data,[23] Gevo asserts that the SE26E6 "enzyme has a catalytic efficiency for NADH that is 172-fold higher than its catalytic efficiency for NADPH." (D.I. 611 at 38) Gevo maintains that its strains show some ancillary usage of NADPH, but disputes Butamax's characterization and testing of the usage of NADPH by its strains. (D.I. 611 at 47-48) To refute Dr. Brown's conclusions from his experiments, Gevo argues that Dr. Brown used different parameters to run the Arfin & Umbarger assay and engineered the parameters to "force the assay to produce his desired results."[24] (D.I. 611 at 47-48)

As is often the case, the parties to this dispute rely on different data obtained by different means to illustrate their respective infringement arguments. Butamax supports

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between 50 percent and 100 percent." He further testified that "70/30" would be "fairly interchangeable" and there would be a "gray area" that "[w]ell, the gray area might be between discriminations of 3 to 1 and 10 to 1, perhaps." (D.I. 648 at 31; D.I. 597, ex. A at 380:18-381:25) Importantly, Dr. Kirsh was contemplating a competitive binding experiment when describing enzymes using nearly exclusively NADPH. (D.I. 597, ex. A at 386)

[23]Gevo supports the statement that its strains are NADH dependent with data and measurements "of K_{cat}/K_m, referred to as the 'catalytic efficiency' of an enzyme." (D.I. 611 at 34-39; D.I. 612 at ¶¶ 49, 89) This measurement and the use of K_m is present in many of the references cited by both parties. *See, e.g.,* Carol Larroy et al., *Characterization of the* Saccharomyces cerevisiae *YMR318C (ADH6) gene product as a broad specificity NADPH-dependent alcohol dehydrogenase: relevance in aldehyde reduction*, 361(1) Biochemical J., 163 (2002) ("Larroy 2002"); Kiritani; Dumas (1992 and 1989); Xing; and, BRENDA database. Butamax's expert, Dr. Rabinowitz, used K_m. *See supra* note 4.

[24]Dr. Brown testified that he used higher amounts of enzyme and lower temperatures to perform his assay than as described in the Arfin & Umbarger assay. (D.I. 611 at 47-48; D.I. 613 at ex. 73 at 148: 2-4; 148:19-149: 9; 130:19-25)

its infringement position with three sources of data: (1) the 0.026 units/mg value taken from a single experiment in *E. coli*, the purpose of which was not related to determining NADH/NADPH dependency; (2) Dr. Brown's assay showing statistically significant activity with NADPH; and (3) Gevo's published data showing a 6 to 1 (for strain SE26E6) and 8 to 1 (for strain P2D1A1) preference for NADH to NADPH, using specific activities. In contrast, Gevo's expert disputes both the design of Dr. Brown's assay and the interpretation of the results. Further, using the same published data, Gevo has compared the catalytic efficiencies of its lead strains as between NADH and NADPH, demonstrating a 172-fold difference in efficiency for NADH.

While Butamax's evidence of infringement is less than compelling, nonetheless, the court finds it sufficient to withstand Gevo's motion for summary judgment, as it raises genuine issues of material fact as to how a person of ordinary skill in the art at the time the invention was made would determine NADH-dependency.[25] Therefore, the parties' motions for summary judgment are denied in this regard.

Gevo also moves for summary judgment of no infringement under the doctrine of equivalents, asserting that its NADH-dependent enzyme is not equivalent to an

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[25]The court notes that metabolic engineering, including cofactor engineering, is a recognized area of research. (*See, eg.,* D.I. 603 ex.17, Stephanopoulos et al, *Metabolic Engineering: Principles and Methodologies* (1998)); *see also*, Sonia Cortassa et al., *An Introduction To Metabolic And Cellular Engineering* (2d ed. 2012); *The Metabolic Pathway Engineering Handbook: Fundamentals* (Christina Smolke, ed., 1st ed. 2010). In this research area, cofactor dependency is extensively analyzed. The term of art, cofactor-dependent (i.e., NADPH-dependent and NADH-dependent), is replete in the scientific literature, the EC databases, and in the parties' references. (*See, e.g.*, Larroy (2002 and 2003); Dumas (1989 and 1992); Xing; and BRENDA database) However, the court does not find a quantification for this term in the parties' documents and, therefore, does not define it herein, but leaves the explanation of this term of art at trial to the parties' scientific experts.

NADPH-dependent enzyme. (D.I. 610; D.I. 611 at 43-44) Butamax alleges that the doctrine of equivalents should apply because "the use of NADH as an electron donor is insubstantially different from the use of NADPH." (D.I 648 at 33) For the reasons discussed above in claim construction, the court does not agree that NADH and NADPH are insubstantially different.[26] *See supra* part III.B; *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 955-56 (Fed. Cir. 2006) (holding that a patented device claiming a particular part with a convex shape was not infringed under the doctrine of equivalents by a similar device using a part with a concave shape, even though the device could function with either a convex or concave portion); *Novartis Pharms. Corp. v. Eon Labs Mfg., Inc.*, 363 F.3d 1306, 1312 (Fed. Cir. 2004) (affirming summary judgment of no infringement under the doctrine of equivalents because this would vitiate one of the claimed requirements of the patent); *Zelinski v. Brunswick Corp.*, 185 F.3d 1311, 1317 (Fed. Cir. 1999) (finding that the district court's grant of summary judgment was proper where the only evidence on infringement under the doctrine of equivalents was a conclusory statement of plaintiff's expert). The court grants Gevo's summary judgment of no infringement under the doctrine of equivalents.[27]

B. Invalidity

1. Anticipation

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[26]For example, a quadruple mutant was needed in order to change an enzyme from NADPH-dependent to NADH-dependent. *See supra* part III.B.2.

[27]The court declines to address prosecution history estoppel, having found that there is no plausible doctrine of equivalents argument.

Gevo contends that the '889 patent is invalid as anticipated. (D.I. 598) More specifically, claim 1 is expressly and inherently anticipated by Larroy (2003) and inherently anticipated by Yocum and Elischweski.[28] (D.I. 599 at 11) Gevo begins with the assertion that "[t]he existence and operation of the five-step isobutanol biosynthetic pathway recited in [claim 1] was known in yeast . . . for decades." (D.I. 599 at 3) Production of isobutanol is an inherent property of the recombinant yeast, as evidenced by references showing isobutanol production in non-recombinant yeast. (D.I. 9-10) Further, Gevo argues that "the prior art included many references that disclosed yeast microorganisms that recombinantly expressed one or more enzymes of the claimed five-step pyruvate-to-isobutanol pathway." (D.I. 599 at 11) Larroy (2003) expressly discloses the production of isobutanol by a recombinantly engineered enzyme. (D.I. 599 at 12-13) Yocum and Elischweski also disclose the construction of recombinant yeast, which overexpress certain of the five enzymes. (D.I. 599 at 15-16) Gevo contends that the references do not have to demonstrate isobutanol production, as anticipation requires only an enabling disclosure. (D.I. 650 at 12,16) Gevo asserts that even under the court's construction that the pathway is contiguous, these three references inherently anticipate claim 1. (D.I. 599 at 17-18)

Butamax responds that none of these references describes expression of all five enzymes identified in the five-step biosynthetic pathway disclosed in claim 1. (D.I. 623

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[28]Larroy (2003)" is Carol Larroy et al., *Properties and functional significance of* Saccharomyces cerevisiae *ADHVI*, 143-144 Chemico-Biological Interactions, 229-238 (2003). "Elischweski" is Elischweski et al., U.S. Patent No. 6,787,334, issued September 7, 2004. "Yocum" is Yocum et al., U.S. Patent Application Publication No. 2004/0146996 A1, published July 29, 2004.

at 32) Moreover, there is no evidence that yeast in general, or in the prior art references, "necessarily" produce isobutanol, let alone through the five-step pathway. (D.I. 623 at 33-34) Butamax asserts that Gevo's evidence through three references regarding natural, nonrecombinant yeast cannot be used to show that genetically engineered yeast in the prior art would inherently produce isobutanol through the five-step pathway, thus defeating inherency. (D.I. 623 at 36-37) Butamax's expert explains that even if all the enzymes have been characterized in native yeast, this does not establish that they work together in a five-step biosynthetic pathway in recombinant yeast because the enzymes must be expressed properly at the same time and in the same place for this to occur. (D.I. 623 at 39, 45) Similarly, Butamax argues that Yocum and Elischweski teach the genetic manipulation of microorganisms for the production of pantothenate, not isobutanol. (D.I. 623 at 45-50) For both of these references, Butamax argues that Gevo improperly seeks to rely on post-filing references as another layer to complete its theory. (D.I. 623 at 48-49)

The court recognizes that the prior art discloses that isobutanol is produced during fermentation. Indeed, Larroy (2003) expressly discloses isobutanol production as a product of recombinant yeast fermentation. The court has construed the term "engineered isobutanol pathway" to require that one or more enzymes in the pathway be engineered. The prior art references disclose genetically engineering one or more enzymes in the pathway. Butamax's argument that the references do not specifically disclose isobutanol production is of no consequence as inherency does not require recognition of the inherent element before the critical date. *Crown Packaging Tech., Inc. v. Ball Metal Beverage Container Corp.*, 635 F.2d 1373, 1383 (Fed. Cir. 2011)

(citations omitted); *accord Schering Corp. v. Geneva Pharms. Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). The court finds that Gevo has raised a substantial question regarding whether claim 1 is inherently anticipated by the prior art. There remain factual disagreements between the parties, however, as to whether the references disclose each and every claim limitation sufficient to find inherent anticipation. As the court must draw all reasonable inferences in favor of Butamax, the court denies Gevo's motion for summary judgment of invalidity as to claim 1 of the '889 patent. For the same reasons, the court also denies Butamax's summary judgment motion of no anticipation.

2. Obviousness

Gevo contends that claims 1-4, 13-15, 17-25, and 34-36 of the '188 patent and claims 1-7, 9-11, 12, 14-19 of the '889 patent are invalid for obviousness in view of the combination of Boulton[29] with other prior art references.[30] Butamax asserts that Gevo's obviousness arguments do not rest on "analogous art." (D.I. 623 at 14) The court disagrees. Analogous art encompasses references "not within the field of the inventor's endeavor, . . . [if it] is reasonably pertinent to the particular problem with which the inventor is involved. *In re Klein*, 647 F.3d 1343, 1348 (Fed Cir. 2011) (citation omitted). The patents-in-suit state that "[i]sobutanol is produced biologically as a by-product of yeast fermentation," acknowledging that yeast fermentation is related and relevant.

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[29]"Boulton" is Chris Boulton & David Quain, *Brewing Yeast & Fermentation*,113-21 (Blackwell Science Ltd. 2001).

[30]The combination references will be introduced as needed for the court's analysis.

('188 patent, 1:39-40; '889 patent, 1:39-40) The patents also refer to and discuses "fusel oil" in the context of "beverage fermentation." ('188 patent, 1:39-62; '889 patent, 1:39-62) The patents-in- suit cite to at least one article from the applied brewing and fermentation arts. ('188 patent, 1:51-52; '889 patent, 1:51-52)

Butamax next argues that "nothing would lead a [person of ordinary skill in the art] to combine a reference about trace amounts of flavor components in beer with knowledge about genetic engineering to make isobutanol." (D.I. 623 at 14) This argument is contrary to the references to beverage fermentation in the patents and to Butamax's expert's research.[31] Statements in the cited references, such as "manipulation of the concentrations of individual higher alcohols is possible via genetic modification of yeasts," also refute this argument. (D.I. 650 at 25 (citing Boulton, at 121))

Gevo contends that the five-step pyruvate to isobutanol pathway is described in the prior art. (D.I. 599 at 3-4) Specifically, Gevo's expert, Dr. Stephanopoulos, refers to Boulton as a prior art reference disclosing the pathway and each of the enzymes.[32] (D.I. 599 at 4; D.I. 683 at ¶¶ 41-44) Dr. Stephanopoulos concluded that "the scientific

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[31]Butamax's expert, Dr. Henry, cites to beverage fermentation in an article she co-authored on research directed at the ethanol fuel industry. (D.I. 650 at 26; D.I. 651, ex. 130, Erin L. Krause, et al., *Determining the effects of inositol supplementation and the* opi1 *mutation on ethanol tolerance of* Saccharomyces cerevisiae, 3 Industrial Biotechnology, 260-68, ref. 12, 22 (2007), at 10)

[32]Gevo also points to several other references including A. Dinsmoor Webb & John L. Ingraham, *Fusel Oil, in*, 5 *Advances in Applied Microbiology* 317 (1963); C. Rainbow, *Brewers' Yeast*, in 3 *The Yeasts*, 147 (A. H. Rose and J. S. Harrison, eds, 1970); E. Chen, *Formation and Analysis of Fusel Alcohols in Beer*, (1977) (Doctoral Thesis, McGill University, Montreal: Canada)

literature concerning the natural production of higher alcohols such as isobutanol from yeast demonstrates that these products are produced from the α-keto acid intermediate that is derived from two sources: amino acid catabolism and biosynthesis from pyruvate." (*Id.* at ¶ 49) Butamax's expert, Dr. Henry, opines that "Boulton does not provide any data confirming or tracing the intermediates in the purported pathway or show that the identified enzymes are expressed in such a manner to form an actual functional pathway." (D.I. 623 at 18; D.I. 625, ex. LLL at ¶¶ 53-56, 84-89) Instead, Dr. Henry avers that "Boulton expressly acknowledges that the purported metabolic pathways are not entirely understood . . . ." *Id.* at ¶ 54) Butamax alleges that the addition of other references does not illuminate the issue. Dr. Henry does not agree that the other references show that the five-step pathway occurs naturally in yeast. (D.I. 625, ex. LLL at ¶¶ 84) In particular, Dr. Henry questions whether the references show each step and the enzyme involved. (*Id.*) As each expert interprets the scientific literature differently, there is a factual disagreement on whether the prior art renders the independent claims of the '188 and '889 patent obvious.

Setting aside Butamax's general argument that there is no motivation to combine the beverage fermentation references with recombinant engineering references, the experts next disagree on whether the references teach recombinantly overexpressing one or all of the enzymes in the five-step pathway to increase isobutanol production. Dr. Henry opines that Yocum teaches away from the engineered pathway in claim 1 of the '188 patent. (D.I. 625, ex. LLL at ¶¶ 91) Dr. Stephanopoulos opines that recombinant engineering techniques existed and, "because it was also known that increasing expression of a component of a pathway would enhance production of the

end product above background levels, expressing genes encoding pathway enzymes to increase levels of the end product above background levels would have been obvious to those of ordinary skill in metabolic engineering." (D.I. 683 at ¶¶ 80-82) Whether or not it was obvious to combine the recombinant references with Boulton is a question of fact, not appropriate for decision on summary judgment. For these reasons and in light of the clear and convincing burden needed to find invalidity, the court denies Gevo's motion for summary judgment of invalidity as to the obviousness of the asserted claims of the '188 and '889 patents and Butamax's motion for partial summary judgment of no invalidity.

3. Written description

a. Indefiniteness

Gevo contends that claim 8 of the '889 patent is indefinite. (D.I. 599 at 31) Butamax filed a cross-motion for summary judgment that claim 8 is not indefinite as a matter of law. (D.I. 623 at 20) Claim 8 limits independent claim 1, adding that "the microorganism produces isobutanol as a single product." ('889 patent, 326:21-22) Butamax argues that, as both parties have agreed that the term "single product" is capable of being construed, Gevo cannot contend that the term and claim are indefinite. At this stage of the proceedings, Gevo's proffer of a claim construction does not foreclose its argument that the claim is indefinite.

Both parties agree that in fermentation, an organism would not produce a single product to the exclusion of all others. (D.I. 599 at 32; D.I. 623 at 54) Butamax argues that "single product" is measurable as different from a "by-product" or as distinguishing

the patent from "the traditional processes whereby isobutanol was produced as a component of 'fusel oil' or as part of a mixture with acetone and ethanol." (D.I. 623 at 53-54) Gevo frames the question as "how much non-isobutanol fermentation product does a microorganism need to produce in order for the isobutanol production to no longer be considered a 'single product' of the microorganism?" (D.I. 599 at 32) Butamax avers that "substantial" is sufficiently clear to one skilled in the art to render the claim term definite. *See Exxon Research & Eng'g Co. V. United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001). As the court adopted Butamax's construction, the court denies Gevo's motion for summary judgment that claim 8 is indefinite and grants Butamax's motion for partial summary judgment that claim 8 is not indefinite.

b. Enablement and written description

Gevo contends that claim 8 of the '889 patent is invalid for lack of written description and lack of enablement under 35 U.S.C. §112. (D.I. 599 at 33) As discussed above, claim 8 contains the added limitation of "single product." The court determined that the term "single product" could be construed and adopted Butamax's claim construction, that is, "[t]he microorganism produces isobutanol without substantial amounts of other fermentation products." *See supra* part III.C.3.

Gevo argues that the specification does not demonstrate to a person of ordinary skill in the art that Butamax was in possession of a microorganism capable of producing isobutanol as a "single product." (D.I. 599 at 35) In this regard, Dr. Stephanopoulos points out that the highest yield disclosed in the '889 patent was 0.6% according to example 18. (D.I. 599 at 35 (citing '889 patent, tbl.9)) Dr. Stephanopoulos concludes that this yield indicates that other products were being produced in large quantities by

the yeast. (D.I. 599 at 35; D.I. 601 at ¶ 189) Finally, Gevo avers that Butamax could only produce isobutanol at background levels using the methods of the '889 patent and "did not accomplish its own target laboratory yields for at least three years after the '889 application was filed." (D.I. 650 at 31)

Butamax's expert contends that the recombinant yeast cells producing more isobutanol than the control strains shows that claim 8 is "sufficiently enabled and supported by the written description."[33] (D.I. 623 at 57; D.I. 625, ex. LLL at ¶ 206) Further, Dr. Klibanov opines that any additional experimentation for "refining and optimizing yields" would be routine. (D.I. 623 at 57; D.I. 625, ex. OOO at ¶ 216) Butamax's experts do not respond to Dr. Stephanopoulos' contentions that Butamax could not produce "commercial levels" of isobutanol or that it had not achieved its own production goals. (D.I. 650 at 39; D.I. 652 ¶ 208)

"Enablement does not require an inventor to meet lofty standards for success in the commercial marketplace. Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338 (Fed. Cir.2003); *cf. Atlas Powder Co. v. E.I. du Pont De Nemours*

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[33]Butamax's expert, Dr. Henry, explains that the specification of the '889 patent "shows that recombinant yeast cells expressing an engineered isobutanol biosynthetic pathway produced substantially more isobutanol than the control strains." (D.I. 625, ex. LLL at ¶ 206 (citing '889 patent, example 18, 42:60-44:33)) The concentration of isobutanol recovered from the experiments shown in the examples varies widely - from 0.4 mM to 1.2 mM of isobutanol produced from *E.Coli* strains grown on glucose versus no detected isobutanol in the control strains (*see* '889 patent, example 15 & tbl.5) and from 0.20 mM to 0.97 mM, for isobutanol produced by *Saccharomyces cervisiae* on glucose versus 0.11-0.12 mM for the control (*see* example 18, tbl.9).

& Co., 750 F.2d 1569, 1577 (Fed. Cir.1984) (patentee's experiments designated as "failures" because they were "not optimal under all conditions" did not establish nonenablement; "such optimality is not required for a valid patent"). As Butamax did not claim a commercially viable product, it is of no consequence whether the patent enables such a product.

The question of undue experimentation is a matter of degree and the amount of experimentation may not be "unduly extensive." *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1253 (Fed. Cir. 2004) *(quoting PPG Indus., Inc. v. Guardian Indus., Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996)). Experiments involving repetition of known or commonly used techniques do not necessarily render the experimentation "undue". *See Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998) (finding that the difficulty in experimentation was not due to shortcomings in the patent disclosure, but due to the difficulty in producing certain antibodies using techniques commonly requiring repetition). It is important to note that the "test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance . . . ." *PPG Indus., Inc.*, 75 F.3d at 1564 (citation and quotation omitted).

"Permissible experimentation is, nevertheless, not without bounds." *Cephalon, Inc. v. Watson Pharmaceuticals, Inc.*, --- F.3d ----, 2013 WL 538507 at *6-7, (Fed. Cir. 2013); *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003) (finding the amount of experimentation excessive where the specification taught away from the claimed subject matter and there was evidence of the patentee's own failures to make

and use the later claimed invention at the time of the application); *White Consol. Indus., Inc. v. Vega Servo–Control, Inc.*, 713 F.2d 788, 791 (Fed. Cir. 1983) (holding experimentation was unreasonable, where one and a half to two years' work was required to practice the patented invention).

There is a genuine issue of material fact about whether a showing of increased isobutanol production in recombinant yeast over controls is sufficient to enable a claim of producing isobutanol as a "single product;" i.e., when a yield for a product is low, there are necessarily other products present. The parties' experts disagree on the amount of product necessary to meet the "single product" claim term and how much isobutanol could be produced by the methods of the '889 patent. Butamax argues that refining the yields for isobutanol would involve routine additional experiments. Gevo has not proffered evidence that the specification would not allow a person of ordinary skill in the art to understand the claimed invention. As Gevo's burden is one of clear and convincing evidence, the court denies Gevo's motion for summary judgment of invalidity of claim 8 for lack of enablement and written description, and also denies Butamax's cross-motion for partial summary judgment of no invalidity of claim 8 for lack of enablement and written description.

Gevo next contends that claims 12 and 13 of the '889 patent are invalid for lack of written description under 35 U.S.C. §112. (D.I. 599 at 35) Claim 12 and 13 read:

> 12. The recombinant yeast microorganism of claim 1 wherein the said microorganism further comprises inactivated genes thereby reducing yield loss from competing pathways for carbon flow.

> 13. The recombinant yeast microorganism of claim 12, wherein said inactivated genes reduce pyruvate decarboxylase activity.

('889 patent, 326:29-36) The '889 patent does not contain a description or examples of a recombinant yeast microorganism with inactivated genes to reduce yield loss from competing pathways for carbon flow or to reduce pyruvate decarboxylase activity ("PDC"). (D.I. 599 at 36) The '889 mentions inactivation of genes only once: "The microbial host also has to be manipulated in order to inactivate competing pathways for carbon flow by deleting various genes. This requires the availability of either transposons to direct inactivation or chromosomal integration vectors." ('889 patent, 16:55-59) Gevo argues that the '889 "patent does not identify any microbial host, any examples, any pathways, or any specific genes that could be inactivated in order to achieve" the goals of claims 12 and 13. (D.I 599 at 37-38) Gevo also asserts that Butamax may not rely on the citation to Dickinson[34] in the specification as support for these claims as it (1) was not incorporated by reference; (2) was cited in the invention's background section as support for increasing isobutanol production in yeast using L-valine; and (3) does not teach reducing PDC activity to achieve increased isobutanol production. (D.I. 599 at 38-39)

Butamax responds that the patent specification, combined with the knowledge of those of skill in the art, renders these claims sufficiently described.[35] (D.I. 623 at 58)

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[34]"Dickinson" is Dickinson et al., *An Investigation of the Metabolism of Valine to Isobutyl Alcohol in* Saccharomyces cerevisiae, 273(40) J. Biological Chemistry, 25752-25756 (1998).

[35]Butamax's expert, Dr. Klibanov cites to three portions of the specification:

The specification identifies both the problem and the solution. (D.I 623 at 59) Butamax also avers that "the art contained numerous teachings regarding the deletion of PDC genes, including Dickinson." (D.I. 623 at 60)

The dispute at bar lies in whether the portions of the specification cited by Butamax satisfy the written description requirement of § 112 ¶1, that is, are so "full, clear, concise, and exact" that one of skill in the art would be able to use the same. None of the cited portions of the specification provide a description to one of skill in the art on how to construct a recombinant yeast microorganism with "inactivated genes" to reduce "yield loss from competing pathways." Although the specification may be interpreted as identifying both the the problem and the solution, it does not even begin to describe how to put into practice the solution.[36] The court finds that the written description for claim 12 is insufficient.

With respect to claim 13, there is no dispute that the specification of the '889 patent does not specifically disclose "inactivated genes" that "reduce pyruvate

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- "α-Ketoisovalerate can be converted to isobutyraldehyde by a number of keto acid decarboxylase enzymes, such as for example pyruvate decarboxylase. To prevent misdirection of pyruvate away from isobutanol production, a decarboxylase with decreased affinity for pyruvate is desired. ('889 patent, 12:12-17)
- The microbial host also has to be manipulated in order to inactivate competing pathways for carbon flow by deleting various genes. This requires the availability of either transposons to direct inactivation or chromosomal integration vectors. ('889 patent, 16:55-59)
- Citation to Dickinson, explaining the Ehrlich pathway. ('889 patent, 1:46-47)

[36]Butamax attempts to rescue this argument stating,"brevity should be lauded, not punished." (D.I. 623 at 59) The information as to how to construct the claimed recombinant yeast microorganism is not brief; it is non-existent.

decarboxylase activity." ('889 patent, 326: 35-36) Again, the dispute is whether the portions of the specification cited by Butamax nevertheless satisfy the written description requirement. The specification identifies two enzymes which have "decreased affinity for pyruvate," but there is no discussion about gene inactivation or about PDC in that context. ('889 patent, 12:17-23) The generic suggestion to inactivate competing pathways does not teach anything specific about reducing PDC activity by inactivating those genes. ('889 patent, 16:55-57) The citation to Dickinson ('889 patent, 1:46-47) does not provide adequate written description. Said reference is neither incorporated by reference, nor is it cited in the '889 patent in the context of deleting PDC genes. Instead it is used to support the specification's description of the Ehrlich pathway in the background section. ('889 patent, 1:39-47) Further, this reference analyzes the metabolism of valine to isobutyl alcohol and describes yeast strains that have three PDC genes deleted. It states that the "route, via pyruvate decarboxylase, is the one that is used because elimination of pyruvate decarboxylase activity in a . . . triple mutant virtually abolished isobutyl alcohol production" and "a single pyruvate decarboxylase isozyme is all that is required for isobutyl alcohol formation from valine," effectively teaching away from the meaning of claim 13. (D.I. 603, ex. 35 at 25751, 25755) Even if Butamax had incorporated this reference to support claim 13, it does not supplement the specification in such a way as to provide a sufficient written description.

The court concludes that the specification of the '889 patent does not provide a sufficient written description of claim 13. For these reasons, the court grants Gevo's

motion for summary judgment of invalidity of claims 12 and 13 for lack of written description and denies Butamax's cross-motion of no invalidity.

C. Excluding Expert Testimony

Rule 702 of the Federal Rules of Civil Procedure allows a qualified witness to testify in the form of an opinion if the witness' "scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue" and if his/her testimony is the product of reliable principles and methods which have been reliably applied to the facts of the case.

Butamax moves to exclude the testimony and reports of Gevo's expert, Dr. Stephanopoulos, on inherent anticipation of the '889 patent. (D.I. 641) Butamax contends that Dr. Stephanopoulos based his analysis on "the incorrect legal construct that inherent anticipation can be found when the prior art 'possibly' practices the claimed invention." (D.I. 641 at 2) Gevo argues that the "prior art reference need not practice the claims all the time under every conceivable condition." (D.I. 683 at 6) The court concludes that, at most, the standard for finding inherent anticipation was not eloquently articulated in Dr. Stephanopoulos' expert report. Reading the articulated standard as a whole, Dr. Stephanopoulos applied the correct standard.[37] (D.I. 683, ex. A at ¶ 18); *Glaxo Group Ltd. v. Teva Pharms.*, Civ. No. 02-219, 2004 WL 1875017, at *19 (D. Del. Aug. 20, 2004) ("Although inherent anticipation does not require the

[37]In part, he explained that, "[w]hat matters for anticipation is that all elements of a patent claim are present at the same time, at any time, in the prior art. If this requirement is satisfied, I understand that the prior art anticipates the claim even if, under some conditions, the same article described in the prior art sometimes does not have all the elements of the claim." (D.I. 683, ex. A at ¶ 18)

element to be present each and every time, it does require the result to be a necessary and inevitable consequence of practicing the invention claimed in the prior art under normal conditions.").

Butamax's repeated arguments that Dr. Stephanopoulos did not independently conduct experiments as part of his analysis are of no consequence. (D.I. 641 at 4) By analogy, "[a] patentee may prove . . . infringement by either direct or circumstantial evidence. There is no requirement that direct evidence be introduced." *Liquid Dynamics Corp. v. Vaughan Co.*, 449 F.3d 1209, 1219 (Fed. Cir. 2006) (citing *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1272 (Fed. Cir. 1986) (abrogated on other grounds)). Dr. Stephanopoulos formed his opinions based on scientific literature and was not required to retest the results and methods detailed therein.[38]

Butamax also argues that "Dr. Stephanopoulos extrapolates from statements made in references alleging that isobutanol is sometimes produced in non-recombinant yeast to conclude that the recombinant yeast in the prior art would necessarily produce isobutanol." (D.I. 641 at 10-11) According to Butamax, this "sometimes" production renders Dr. Stephanopoulos' opinions improper as a matter of law and would be misleading and confusing to a jury. (D.I. 641 at 10-11) Gevo responds that the fact that yeast naturally produce isobutanol is a known and well characterized property of

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[38]To put Butamax's protests to rest, expert testimony was excluded in *Izumi*, when the theory advanced was not based on testing, literature references or any other scientifically recognized data. The court found that the expert's theory was "based solely on his subjective belief." *Izumi Prods. Co. v. Koninklijke Philips Elecs. N.V.*, 315 Fr. Supp. 2d 589, 602 (D. Del. 2004).

yeast. (D.I. 683 at 8) Gevo avers that extrapolating from natural yeast to recombinant yeast is proper under normal fermentation conditions, identifying "several references In which the claimed isobutanol pathway was genetically engineered to overexpress one of the enzymes in the pathway." (D.I 683 at 10) The court denies Butamax's motion to exclude Gevo's expert, Dr. Stephanopoulos's opinions on inherent anticipation.

V. Conclusion

For the foregoing reasons, the court denies Butamax's summary judgment motion of infringement and grants Gevo's cross-motion for summary judgement of no infringement. The court denies in part and grants in part the parties motions regarding validity. The court denies Butamax's motion to exclude Gevo's expert's testimony with regards to the '188 patent. The court reserves its decision on Butamax's motion to exclude expert testimony on the '376 patent.

An appropriate order shall issue.

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

BUTAMAX™ ADVANCED BIOFUELS LLC,	)	
Plaintiff/Counterclaim Defendant	)	
v.	)	Civ. No. 11-54-SLR
GEVO, INC.,	)	
Defendant/Counterclaim Plaintiff	)	
v.	)	
E.I. DU PONT DE NEMOURS AND COMPANY,	)	
Counterclaim Defendant	)	

ORDER

At Wilmington this 19th day of March, 2013, consistent with the memorandum opinion issued this same date;

IT IS ORDERED that:

1. Butamax's summary judgment motion of infringement of the '188 and '889 patents (D.I. 595) is denied.

2. Gevo's motion for summary judgment of non-infringement of the '188 and '889 patents (D.I. 610) is granted in part and denied in part. The motion is granted as to no infringement under the doctrine of equivalents.

3. Gevo's motion for summary judgment of invalidity (D.I. 598) is granted in part

and denied in part. The motion is granted as to the invalidity of claim 12 and 13 of the '889 patent for lack of written description and enablement.

4. Butamax's cross-motion of no invalidity of the '889 patent (D.I. 622) is granted in part and denied in part. The motion is granted as to no invalidity of claim 8 for indefiniteness.

5. Butamax and DuPont's motion to exclude testimony by Gevo's experts with respect to the '188 patent and '376 patent is denied as it relates to the '188 patent. (D.I. 640) The court reserves its decision as it relates to the '376 patent.

United States District Judge

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BUTAMAX(TM) ADVANCED BIOFUELS LLC,	)	
Plaintiff,	)	
v.	)	C.A. No. 11-54-SLR
GEVO, INC.,	)	
Defendant,	)	

AMENDED FINAL JUDGMENT

WHEREAS on March 19, 2013, the Court entered a Memorandum Order (D.I. 707, 708) regarding, among other things, motions for summary judgment and claim construction concerning disputed limitations of the asserted claims of the United States Patent Nos. 7,851,188 ("the '188 patent") and 7,993,889 ("the '889 patent"); and held a Final Pretrial Conference on March 20, 2013.

WHEREAS the Court granted-in-part Defendant's Motion for Summary Judgment of invalidity, holding that claims 12 and 13 of the '889 patent are invalid. (D.I. 708 at 1-2).

WHEREAS the Court granted Defendant's Motion for Summary Judgment of no infringement under the doctrine of equivalents. (D.I. 708 at 2).

WHEREAS Plaintiff has stipulated that, subject to its right to appeal all appealable issues, and based on the Court's construction of the disputed limitations "acetohydroxy acid isomeroreductase" of the asserted claims of the '188 and '889 patents, the accused products—Defendant's strains 6293, 7046, 7529, 10557, 11071, 11245—have not literally infringed and do not literally infringe, these patents.

WHEREAS the Court has expressly determined that there is no just reason for delay in entering final judgment on the claims relating to the '188 and '889 patents until final determination of the claims remaining in C.A. No. 11-54-SLR—which relate to the separate claims concerning Gevo's 8,017,375 and 8,017,376 patents—and therefore, in the interest of judicial efficiency, pursuant to Fed. R. Civ. P. 21 the Court severed the claims and defenses relating to the '375 and '376 patents from the above-captioned action.

IT IS HEREBY ORDERED and ADJUDGED this 10th day of April, 2013 that final judgment be and hereby is entered in favor of Defendant Gevo, Inc. and against Plaintiff Butamax™ Advanced Biofuels LLC with respect to the Butamax claims relating to '188 and '889 patents.

United States District Judge

1101611/36429